30th ANNIVERSARY

MARCH 1, 1988

The American Journal of CARDIOLOGY®

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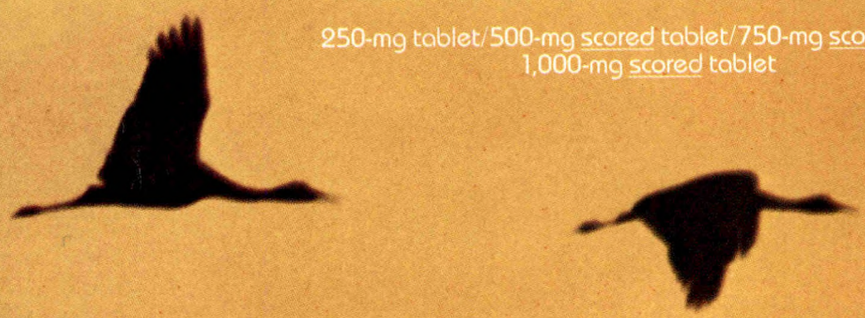

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System-controlled... not skin-controlled[1-4]

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In studies of over 500 anginal† patients treated with Deponit, the large majority showed a reduced frequency of anginal attacks and improved ability to perform everyday activities such as walking, stair climbing and sex. And Deponit efficacy was sustained during these routine activities.[5]

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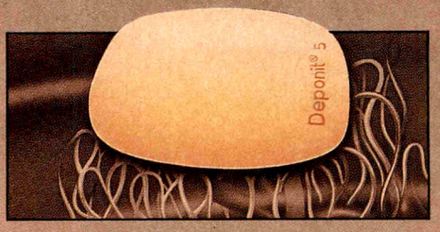

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- Minimal variations in absorption
- No premature release of NTG
- Designed for superior patient acceptance
- Once-a-day dosing, 24-hour delivery
- International record of success

References: 1. Good WR: Transdermal drug delivery systems, in *Drug Delivery Systems*, Springfield, Oregon, Aster Publishing Corporation, 1985, pp 40-48. **2.** Keshary PR, Chien YW: Mechanism of transdermal controlled nitroglycerin administration: II. Assessment of rate-controlling steps. *Drug Development and Industrial Pharmacy* 1984;10:1663-1699. **3.** Black CD, in Rayment CM, ed: *Recent Controversies Involving Transdermal Nitroglycerin Delivery Systems*. Proceedings of a Symposium, New Orleans, Louisiana, 1985, pp 1-13, 1986. **4.** Noonan PK et al: Relative bioavailability of a new transdermal nitroglycerin delivery system. *J Pharm Sci* 1986;75:688-691. **5.** Scheiner SL, Franton B, Yuan W, et al: Evaluation of Deponit®, a transdermal nitroglycerin film in the treatment of angina in clinical practice. Data on file, Wyeth-Ayerst Laboratories.

*"Gradient-charged™" refers to the differential concentration of free and bound NTG, which results in continuous transport and controlled release of free drug at the skin surface.

†Effectiveness of this product has not been established pending final evaluation by FDA (see prescribing information).

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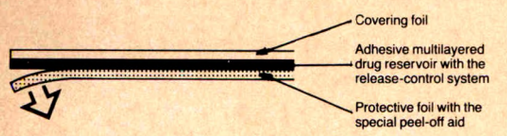
See important information on next page.

WYETH AYERST™

Wyeth-Ayerst®
Deponit®
(nitroglycerin transdermal delivery system)
5 mg/24 hours, 10 mg/24 hours

Description
Deponit® is a unique nitroglycerin-containing transdermal delivery system. A multilayered self-adhesive film, the system contains nitroglycerin in a matrix composed of lactose, plasticizer, medical adhesive, polyisobutylene, and aluminized plastic for controlled release of the active agent through the skin into the systemic circulation. For the 24 hours during which the system is applied to the intact skin, its technology is intended to deliver an accurate dosage with no premature release of the nitroglycerin or undesired accumulation on the skin. Nitroglycerin (glyceryl trinitrate) is a vasodilator for the relief and prevention of anginal attacks.
Deponit® is available in two strengths which release either 5 mg or 10 mg of nitroglycerin during a 24-hour period. The 5 mg/24 hr system has a 16 cm^2 releasing surface and contains 16 mg nitroglycerin. The 10 mg/24 hr system has a 32 cm^2 releasing surface and contains 32 mg nitroglycerin.
The Deponit® system is approximately 0.3 mm thick, insoluble in water, and, as illustrated below, consists of two main elements:
1. A flexible, flesh-colored waterproof covering foil.
2. A multilayered adhesive film that constitutes simultaneously the drug reservoir and the release-control system.



The system is protected by an aluminum foil which has a patented S-shaped opening to facilitate its removal prior to use of the system.

Clinical Pharmacology
When the Deponit® system is applied to the skin, nitroglycerin is continuously released for absorption directly into the systemic circulation. Thus, active drug reaches the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth-muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption, secondary to vascular smooth-muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.
In a bioavailability study using healthy volunteers,[1] transdermal absorption of nitroglycerin from the Deponit® system achieved steady-state venous plasma levels and maintained these levels for 24 hours. Detectable plasma levels were attained within 30 minutes after application of the system and were still detectable 30 minutes after removal of the system.
The amount of nitroglycerin released (5 mg/24 hr or 10 mg/24 hr) represents the mean release rate of nitroglycerin from the system as determined from healthy volunteers, and hence, the amount potentially available through the skin. Absorption will vary among individuals. Precise definition of "therapeutic plasma level" is not known at this time.

Indications and Usage
This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

Contraindications
Nitroglycerin is contraindicated in patients known to be intolerant of organic nitrate drugs and in patients with marked anemia.

Warnings
In patients with acute myocardial infarction or congestive heart failure, nitroglycerin should be used under careful clinical and/or hemodynamic monitoring.
In terminating treatment of patients with angina, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent the sudden withdrawal reactions which are characteristic of vasodilators in the nitroglycerin class.
Transdermal nitroglycerin systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

Precautions
Symptoms of hypotension, such as faintness, weakness, or dizziness, particularly orthostatic hypotension, may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.
Deponit® is not intended for use in treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitrates may be necessary.
PREGNANCY
Pregnancy Category C. Animal reproduction studies have not been conducted with nitroglycerin. It is not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.
NURSING MOTHERS
It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when the preparation is administered to a nursing woman.

Adverse Reactions
Transient headache is the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Deponit® therapy is continued. When such headaches are unresponsive to treatment, the dosage should be reduced or use of the product discontinued.
Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis these symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist, the Deponit® dose should be reduced or use of the product discontinued.

Dosage and Administration
Deponit® can be applied as a single system or as multiples, depending upon the clinical requirements. Dosage should be titrated to achieve the optimal therapeutic effect by monitoring clinical response, side effects, heart rate, and the effect of therapy upon blood pressure.
Deponit® should be removed from the single-unit package just prior to use. The protective aluminum precut S-shaped foil is removed according to the "Patient Instructions," and the system is applied with a firm pressure on a convenient skin site, preferably on the chest, inner side of the upper arm, or shoulders. Deponit® should not be applied to the distal parts of extremities.
Each system is designed to remain in place for 24 hours; however, the treatment site should be changed daily to minimize skin irritation and should be intact, clean, and dry. If necessary, hair may be removed by clipping.
Therapy should be initiated with application of a single Deponit® system, delivering 5 mg every 24 hours. Response in terms of satisfactory control of anginal symptoms without adverse effects should be evaluated to determine the optimal dose. Some patients may require adjustment of dosage to provide a better clinical response. This can be achieved by removing the system delivering 5 mg/24 hours, and applying a larger system delivering 10 mg/24 hours or a multiple of either system, depending on the dose required to achieve the desired effect.
After 24 hours, the system should be removed and discarded. Because no adhesive residue remains on the skin, there is no need to use a solvent.

Storage Conditions
Store at room temperature not above 25°C (77°F). Do not refrigerate.

Patient Instructions for Application
A leaflet describing use of Deponit® is provided with each package.

How Supplied
Deponit® (nitroglycerin transdermal delivery system), Wyeth-Ayerst®, is packaged in cartons containing unit doses of 30 flesh-colored systems on aluminum backings. See table below.

Nitroglycerin released *in vivo*	Total drug content/ system	System size	Carton size
5 mg/24 hrs	16 mg	16 cm^2	30 Systems **(NDC 0008-4195-01)**
10 mg/24 hrs	32 mg	32 cm^2	30 Systems **(NDC 0008-4196-01)**

Caution: Federal law prohibits dispensing without prescription.

Reference
1. Data on file: Wyeth-Ayerst Laboratories Inc., Philadelphia, PA 19101.

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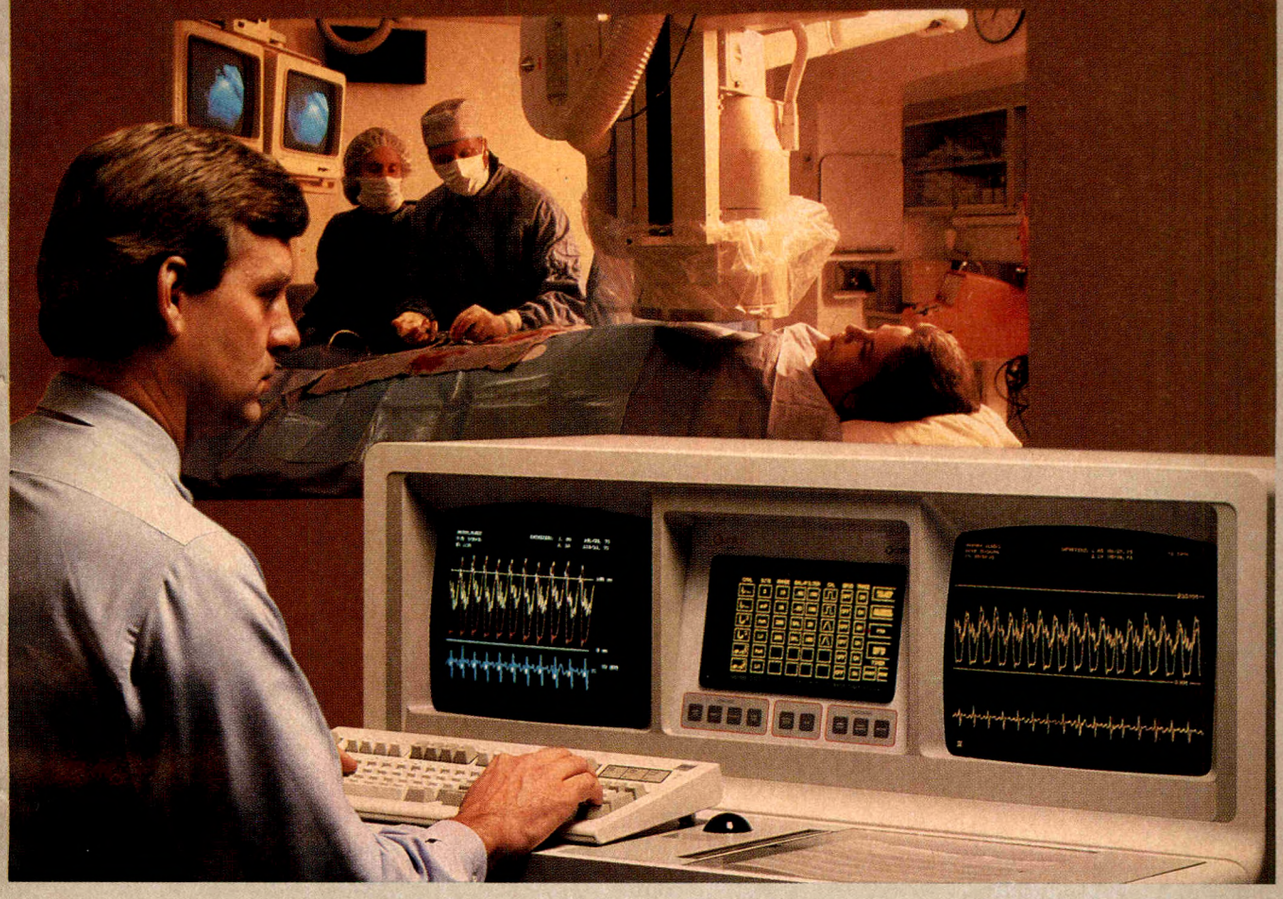

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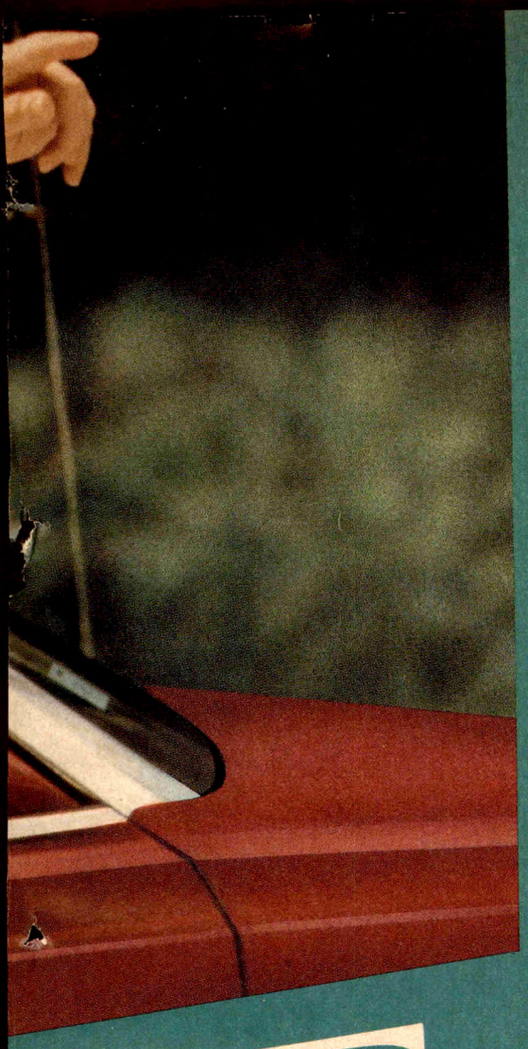
IN HYPERTENSION*

QUALITY

***CAPOTEN® (captopril tablets) may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. Overall, the most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.**

---

1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.
2. Data on file, University of Connecticut.



SQUIBB

Means a feeling of well-being.

Well-being—a feeling difficult to describe when it's present; easy to spot when it's gone. CAPOTEN improved hypertensive patients' sense of general well-being.[1] CAPOTEN had a positive effect on patients' vitality and general health. In fact, all measures of well-being studied showed a trend toward improvement.[2]

These data are based on a multicenter, randomized, 24-week study of 626 mild-to-moderate hypertensive male patients with normal renal function, 181 of whom received captopril.

CAPOTEN—things are looking up for patients who need to keep their blood pressure down.

OF LIFE

THE

CAPOTEN®

(captopril tablets)

DIFFERENCE

QUALITY OF LIFE THE CAPOTEN® (captopril tablets) DIFFERENCE

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia ($< 1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine $\geq$ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $< 1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* – Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* – If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension – Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets.

(J3-658J)

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Intra-Aortic Balloon Pumping.

Because aggressive intervention saves lives.

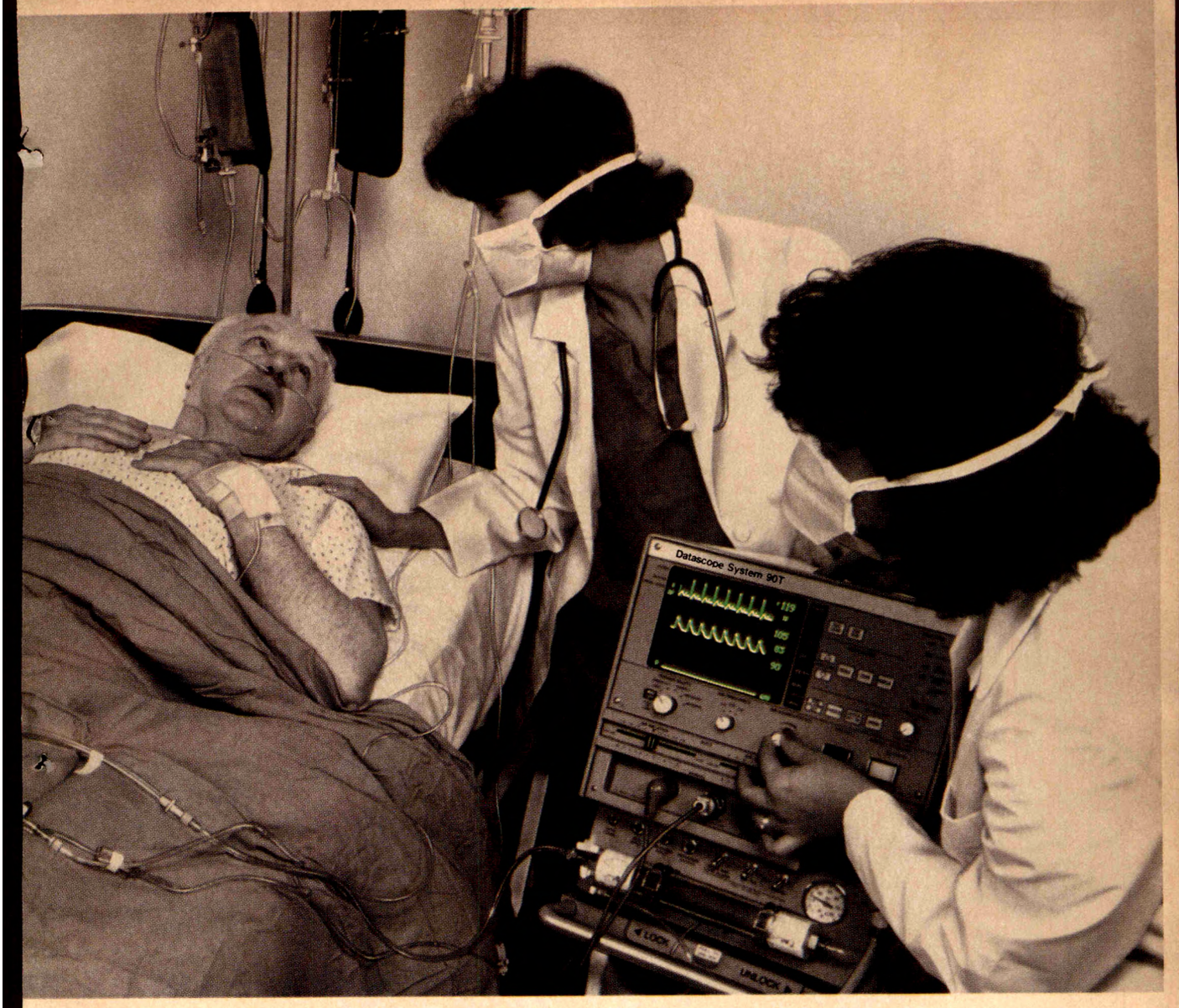
Today hospitals of every size are using IABP to give their patients the greatest possible chance for survival.

More than 70% of all admissions related to ischemic heart disease present at hospitals which do not perform open-heart surgery. In the face of this statistic, hospitals large and small are intervening more aggressively, reducing the mortality rates dramatically. *And intra-aortic balloon pumping is significant in the achievement of these results.*

Datascope has been the innovative force in developing IABP as a life-saving therapy in hospitals of every size. Today, in fact, almost half of all the hospitals we serve do not have open-heart facilities. However, they are aggressively using IABP therapy to support many of their unstable cardiac patients.

A commitment to product innovation.
Since Datascope first introduced IABP in 1969, our resources have been dedicated to its steady development.

The System 90 console and 90T transport balloon pumps



represent fifth generation technology. The simple, automatic operation of these systems has resulted in more Datascope units being put into service than all other pumps combined.

Steady improvements in safety and ease of catheter insertion (from our introduction of the first percutaneous balloon catheter to our newest prefolded 9.5 French dual lumen catheter) have resulted in more aggressive use of IABP therapy at the earliest indication.

Comprehensive educational support.

Datascope's Clinical Education Services Department offers a level of support second to none in IABP, and rare even within the field of cardiac care.

For the many hospitals new to IABP, we work closely with staff members until they are comfortable with every aspect of balloon pumping. We teach theory and practice, including how to use the System 90T to transport patients to hospitals with open-heart facilities.

Our clinical education specialists also work closely with hospitals already providing IABP, conducting seminars and helping them develop their own in-house educational programs.

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With our staff of over 50 technical service representatives dedicated exclusively to your Datascope products, you can depend on us for routine and emergency maintenance 24 hours a day, seven days a week. To make certain you are never without the use of your equipment, loaner units are available. And because there are occasional unplanned demands for IABP, we can help you meet unexpected requirements through our equipment rental program.

You are invited to draw from the many resources of Datascope in the implementation of a new IABP program or in support of your existing program.

For information and assistance, call (201) 265-8800. Or write: Datascope, P.O. Box 5, Paramus, NJ 07653-0005.

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CORONARY ARTERY DISEASE

501 **Effects of Encainide, Flecainide, Imipramine and Moricizine on Ventricular Arrhythmias During the Year After Acute Myocardial Infarction: The CAPS**

The Cardiac Arrhythmia Pilot Study (CAPS) Investigators

The National Heart, Lung, and Blood Institute initiated the Cardiac Arrhythmia Pilot Study (CAPS) to determine the feasibility of suppressing ventricular arrhythmias after acute myocardial infarction. Ten centers enrolled 502 patients younger than 75 years of age with ≥10 ventricular premature complexes (VPC) per hour. Patients were randomized to 1 of 5 treatment tracks with 2 drugs that included encainide, flecainide, imipramine, moricizine and placebo. During a double-blind drug selection phase, drugs or dosage were changed to achieve ≥70% reduction in VPC frequency and >90% reduction in runs of VPC. Patients in the 5 treatment arms were similar in age, sex, clinical characteristics, VPC frequency, left ventricular ejection fraction and concomitant drug treatment. Encainide and flecainide met the CAPS efficacy goals and were well tolerated.

510 **Adoption of Thrombolytic Therapy in the Management of Acute Myocardial Infarction**

Mark A. Hlatky, Harry E. Cotugno, Christopher O'Connor, Daniel B. Mark, David B. Pryor, and Robert M. Califf

A national survey of 1,065 physicians was performed to document use of thrombolytic therapy. Thrombolytic therapy was used in early 1987 by 66% of respondents. Most used intravenous administration, typically 1.5 million units of streptokinase. Duration of symptoms was the key factor in the decision to use thrombolytic therapy; 45% of physicians set a time limit of <4 hours and 85% set a limit of <6 hours. Despite widespread acceptance, however, most physicians used thrombolytic therapy for <25% of their patients with acute myocardial infarction.

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The benefit of antianginal protection plus safety...

CARDIZEM®: A FULLER LIFE

diltiazem HCl/Marion

- ***A remarkable safety profile***[1-6]
  The low incidence of side effects with Cardizem allows patients to feel better.
- ***Protection against angina attacks***[1,5,7-9]
  The predictable efficacy of Cardizem in stable exertional and vasospastic angina allows patients to do more.*
- ***A decrease in myocardial oxygen demand***
  Resulting from a lowered heart rate-blood pressure product.[5]
- ***Compatible with other antianginals***[6†]
- ***Safe in angina with coexisting hypertension, COPD, asthma, or PVD***[1,3,5,6]

60 mg 90/120 mg GREATER DOSAGE FLEXIBILITY

**CARDIZEM® (diltiazem HCl) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.*

†See Warnings and Precautions.

Please see brief summary of prescribing information on the next page.

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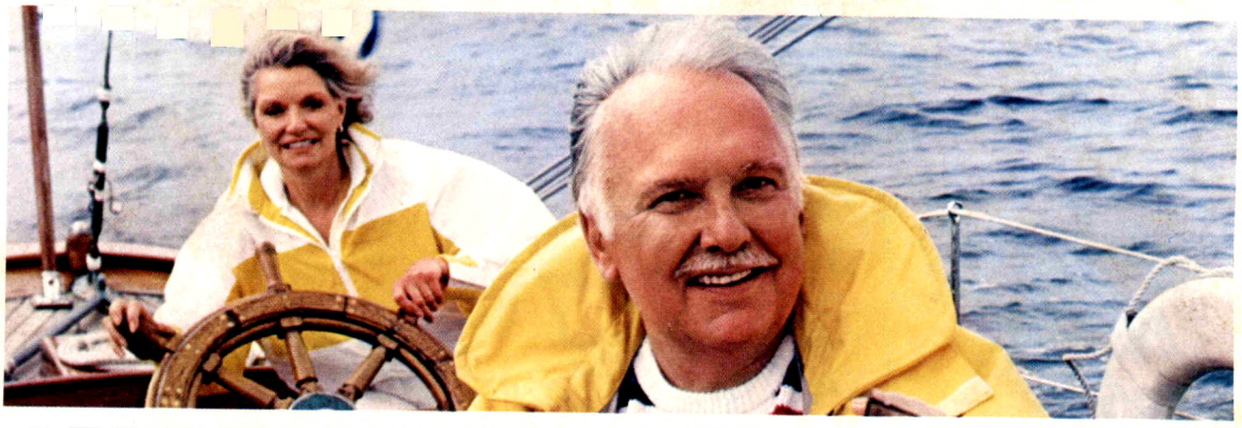

CARDIZEM® ANTIANGINAL PROTECTION PLUS SAFETY

diltiazem HCl/Marion

Usual maintenance dosage range: 180-360 mg/day

BRIEF SUMMARY
Professional Use Information

CARDIZEM®
(diltiazem HCl)
30 mg, 60 mg, 90 mg, and 120 mg Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), and (4) patients who have demonstrated hypersensitivity to the drug.

WARNINGS

1. ***Cardiac Conduction.*** *CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.*
2. ***Congestive Heart Failure.*** *Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.*
3. ***Hypotension.*** *Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.*
4. ***Acute Hepatic Injury.*** *In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)*

PRECAUTIONS

General. *CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.*

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. *Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)*

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: *Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.*

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: *A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.*

Digitalis: *Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)*

Carcinogenesis, Mutagenesis, Impairment of Fertility. *A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.*

Pregnancy. *Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/ postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.*

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. *Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.*

Pediatric Use. *Safety and effectiveness in children have not been established.*

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	*Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.*
Nervous System:	*Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.*
Gastrointestinal:	*Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.*
Dermatologic:	*Petechiae, pruritus, photosensitivity, urticaria.*
Other:	*Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.*

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established. *Issued 6/87*

See complete Professional Use Information before prescribing.

Rx
Cardizem® (diltiazem HCl)
☐ 60 mg ☐ 90 mg
☐ 120 mg
Sig: tid

References: ***1.*** *Schroeder JS: Mod Med 1982;50(Sept):94-116.* ***2.*** *Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39.* ***3.*** *O'Rourke RA: Am J Cardiol 1985;56:34H-40H.* ***4.*** *McCall D, Walsh RA, Frohlich ED, et al: Curr Probl Cardiol 1985;10(8):6-80.* ***5.*** *Frishman WH, Charlap S, Goldberger J, et al: Am J Cardiol 1985;56:41H-46H.* ***6.*** *Shapiro W: Consultant 1984;24(Dec):150-159.* ***7.*** *O'Hara MJ, Khurmi NS, Bowles MJ, et al: Am J Cardiol 1984;54:477-481.* ***8.*** *Strauss WE, McIntyre KM, Parisi AF, et al: Am J Cardiol 1982; 49:560-566.* ***9.*** *Feldman RL, Pepine CJ, Whittle J, et al: Am J Cardiol 1982;49:554-559.*

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515 Trends in Physician Management of Uncomplicated Acute Myocardial Infarction, 1970 to 1987

Mark A. Hlatky, Harry E. Cotugno, Daniel B. Mark, Christopher O'Connor, Robert M. Califf, and David B. Pryor

To document trends in management of uncomplicated acute myocardial infarction, we surveyed 1,065 physicians. Responses were compared with previous surveys of 1970 and 1979. In 1987, patients were kept in the hospital half as long as in 1970, and permitted to resume activities sooner after discharge. Use of coronary angiography has increased, especially in younger patients and those with evidence of jeopardized myocardium. Aspirin and β blocker use has doubled to 80%. The survey documents an increasingly aggressive approach to the patient with uncomplicated acute myocardial infarction.

519 Influence of Long-Term Metoprolol Treatment on Early and Late Exercise Test Performance After Acute Myocardial Infarction

Gunnar Olsson, Nina Rehnqvist, Ulla Freyschuss, and Staffan Zetterquist

In a double-blind randomized study, 154 postinfarction patients treated with metoprolol 100 mg twice daily were compared with 147 patients treated with placebo for 3 years. The effect of study treatment on exercise performance during a 3-year follow-up was evaluated. In the metoprolol-treated group maximal heart rates were significantly reduced ($p < 0.001$) but maximal exercise capacity on a bicycle exercise test was similar. Exercise-induced angina and ST depression early after the infarction were reduced by metoprolol. A multiple logistic regression analysis showed that exercise performance at 6 weeks, male sex, previous infarction, therapy without β blocker and left ventricular heart failure carried independent prognostic information. Further, exercise-induced ST depression ≥ 1 mm in the placebo-treated patients was associated with worsened prognosis. Death, reinfarction or both were significantly reduced by metoprolol treatment in patients with exercise-induced ST depressions ≥ 1 mm at the 6-week test.

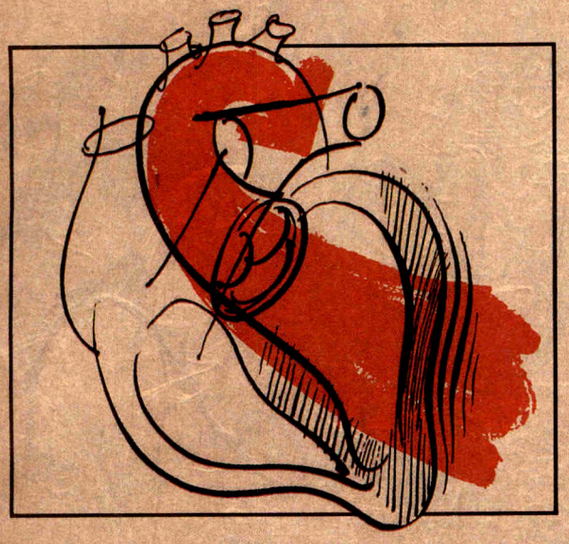
524 Improved Survival up to Four Years After Early Coronary Thrombolysis

Detlef G. Mathey, Joachim Schofer, Florence H. Sheehan, Hans-Joachim Krebber, Marlene Justen, Georg Rodewald, H.T. Dodge, and Walter Bleifeld

Prognosis up to 4 years after thrombolytic therapy for acute myocardial infarction was evaluated in 227 patients. Hospital and 4-year mortality rates were significantly reduced in patients with a patent infarct artery at the end of the acute catheterization. Early bypass surgery in the patent group appeared to improve left ventricular function, and further enhance survival by reducing the incidence of fatal reinfarction and cardiogenic shock.

Continued on page A26

New findings in CHF.



INOTROPY DELIVERS:
Significant increase in ejection fraction compared to an angiotensin-converting enzyme (ACE) inhibitor and placebo.[1]

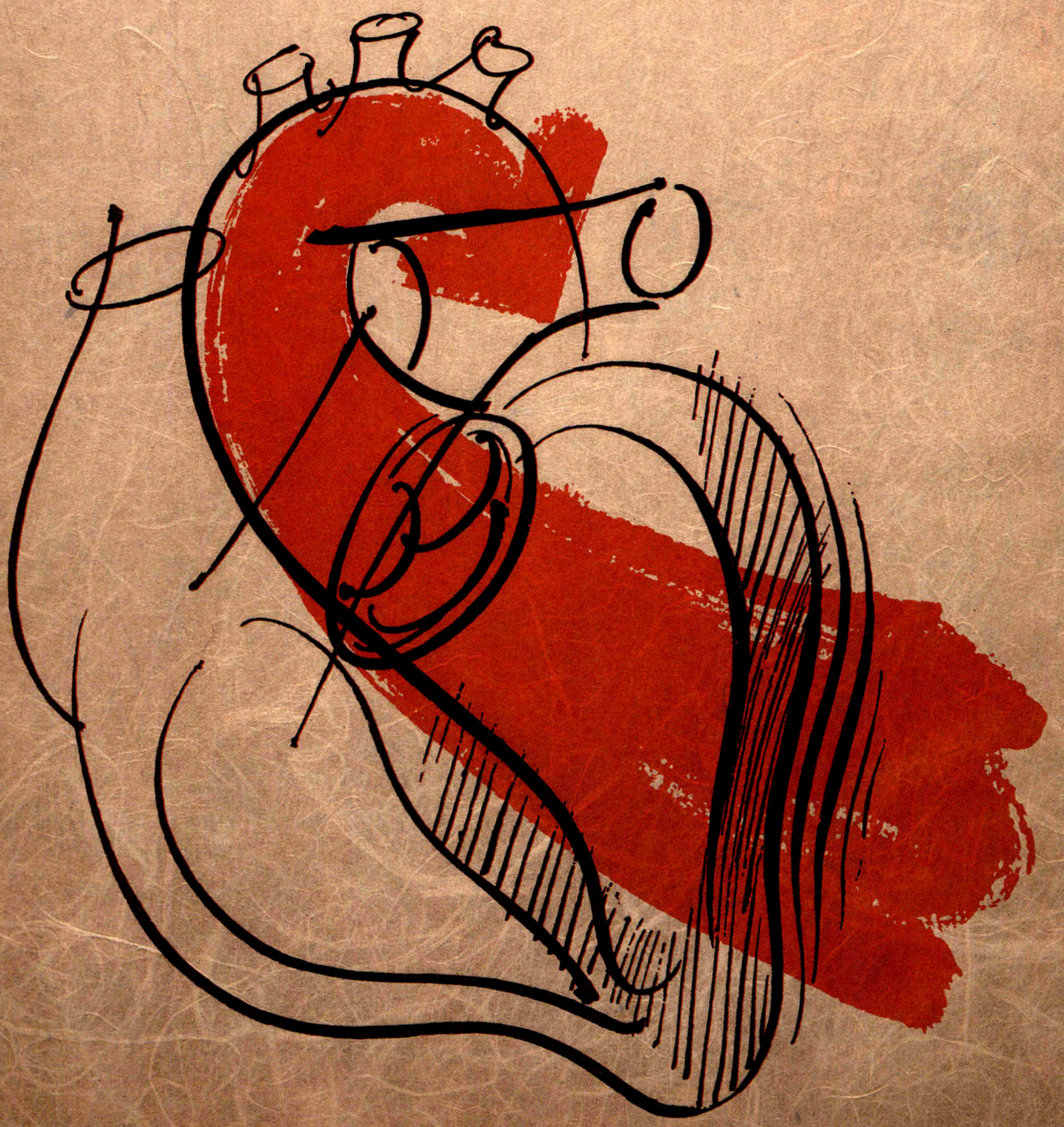
CLINICAL BENEFIT:
Improvement in exercise tolerance not significantly different from ACE inhibitor.[2]

OTHER NEW RESEARCH:
Integral part of all CHF treatment regimens that increased patient survival.[3,4]

See results of new studies on following pages.▶

NEW FINDINGS CONTINUE TO AFFIRM:

LANOXIN®... integral part of regimens that increase survival in CHF patients.[3,4]

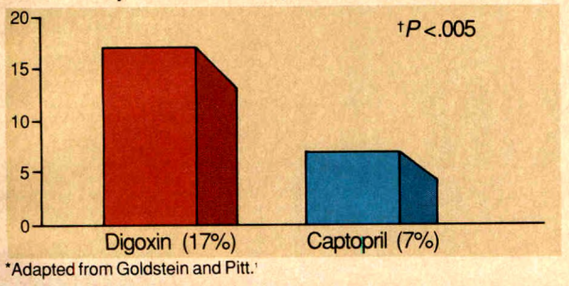


Wellcome

Improves ejection fraction–an important predictor of survival.

In a long-term double-blind study of 300 patients with mild to moderate congestive heart failure, digoxin produced a significant increase in ejection fraction compared to captopril and placebo.[1] Ejection fraction, a measure of ventricular performance, has proven to be an important predictor of survival.[3]

Percent Improvement in Ejection Fraction*†



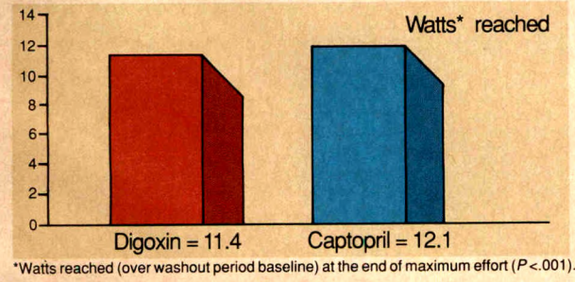
*Adapted from Goldstein and Pitt.[1]

Improves exercise tolerance and cardiac output.

A recent study showed digoxin significantly improved exercise tolerance and O_2 consumption over placebo.[2] Similar results were produced with captopril.[2]

In another study, there was no significant statistical difference between the digoxin and captopril groups in exercise tolerance and functional class.[1] In addition, digoxin has been shown to produce significant improvement in cardiac output in patients at rest as well as during exercise.[5]

Exercise Tolerance–Digoxin vs Captopril[2]



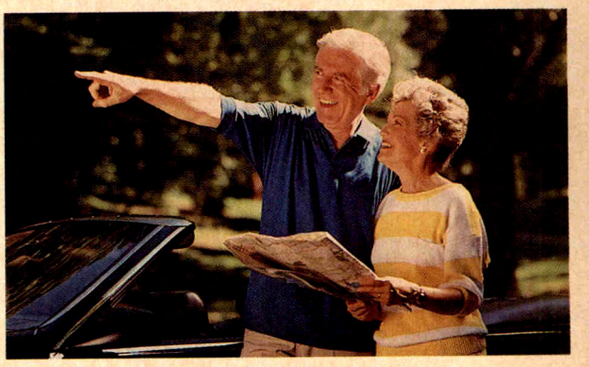
*Watts reached (over washout period baseline) at the end of maximum effort (P <.001).

No difference was observed between the two active treatments. A significant increase in exercise tolerance over respective washout periods was demonstrated.

P 24,168

An integral part of all regimens that increase survival.

In a double-blind trial, patients with chronic congestive heart failure (CHF) undergoing treatment with digoxin and diuretics received additional treatment with prazosin, hydralazine plus isosorbide dinitrate (ISDN), or placebo. The results showed that the combination of digoxin, diuretics, hydralazine, and ISDN was the most effective for maximizing survival in patients with CHF.[3] Similar beneficial effects on mortality were found in the CONSENSUS Trial Study Group when enalapril was combined with diuretics and digoxin.[4]



References: **1.** Goldstein S, Pitt B: Comparison of effects of captopril and digoxin on ejection fraction, exercise tolerance, clinical status, and arrhythmias in patients with mild to moderate heart failure. *J Am Coll Cardiol* 1987;9:203A. **2.** Alicandri C, Fariello R, Boni E, et al: Comparison of captopril and digoxin in mild to moderate heart failure. *Postgrad Med J* 1986;62(suppl 1):170-175. **3.** Cohn JN, Archibald DG, Ziesche S, et al: Effect of vasodilator therapy on mortality in chronic congestive heart failure. *N Engl J Med* 1986;314:1547-1552. **4.** CONSENSUS Trial Study Group: Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med* 1987;316:1429-1435. **5.** Arnold SB, Byrd RC, Meister W, et al: Long-term digitalis therapy improves left ventricular function in heart failure. *N Engl J Med* 1980;303:1443-1448.

IN THE EARLY TREATMENT OF CHF

LANOXIN®
(digoxin) Tablets

Unique support for the failing heart.

See brief summary of prescribing information on the next page.

LANOXIN® (DIGOXIN) TABLETS

125 μg (0.125 mg) Scored I.D. Imprint Y3B (yellow)
250 μg (0.25 mg) Scored I.D. Imprint X3A (white)
500 μg (0.5 mg) Scored I.D. Imprint T9A (green)

Before using Lanoxin Tablets, the physician should be thoroughly familiar with the basic pharmacology of this drug as well as its drug interactions, indications, and usage.

DESCRIPTION: Lanoxin is digoxin, one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium.

INDICATIONS AND USAGE:

Heart Failure: The increased cardiac output resulting from the inotropic action of digoxin ameliorates the disturbances characteristic of heart failure (venous congestion, edema, dyspnea, orthopnea and cardiac asthma).

Digoxin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous fistula, anemia, infection or hyperthyroidism.

Digoxin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies have shown, however, that even though hemodynamic effects can be demonstrated in almost all patients, corresponding improvement in the signs and symptoms of heart failure is not necessarily apparent. Therefore, in patients in whom digoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable renal function or whose potassium levels tend to fluctuate) a cautious withdrawal of digoxin may be considered. If digoxin is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure.

CONTRAINDICATIONS: Digitalis glycosides are contraindicated in ventricular fibrillation.

In a given patient, an untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin. Hypersensitivity to digoxin itself is a contraindication to its use. Allergy to digoxin, though rare, does occur. It may not extend to all such preparations, and another digitalis glycoside may be tried with caution.

WARNINGS: Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs solely for the treatment of obesity is dangerous.

Anorexia, nausea, vomiting and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration. In such circumstances determination of the serum digoxin concentration may be an aid in deciding whether or not digitalis toxicity is likely to be present. If the possibility of digitalis intoxication cannot be excluded, cardiac glycosides should be temporarily withheld, if permitted by the clinical situation.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section in the complete prescribing information).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary and careful monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with severe carditis, such as carditis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS:

General: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, it should be anticipated that dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section in the complete prescribing information).

Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range", because potassium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin.

Hypokalemia may result from diuretic, amphotericin B or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE section).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypercalcemia from any cause predisposes the patient to digitalis toxicity. On the other hand, hypocalcemia can nullify the effects of digoxin in man; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that calcium affects contractility and excitability of the heart in a manner similar to digoxin.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine, verapamil, and amiodarone cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the dose. The effect is mediated by a reduction in the digoxin clearance and, in the case of quinidine, decreased volume of distribution as well.

Certain antibiotics may increase digoxin absorption in patients who convert digoxin to inactive metabolites in the gut (see Pharmacokinetics portion of the CLINICAL PHARMACOLOGY section in the complete prescribing information). Recent studies have shown that specific colonic bacteria in the lower gastrointestinal tract convert digoxin to cardioinactive reduction products, thereby reducing its bioavailability. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation, and may be as much as two-fold in some cases.

Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (e.g. hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity if large doses of digoxin are required. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e. Sick Sinus Syndrome), digoxin may worsen sinus bradycardia or sino-atrial block.

In patients with Wolff-Parkinson-White Syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation.

Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Digoxin may produce false positive ST-T changes in the electrocardiogram during exercise testing.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Laboratory Tests: Patients receiving digoxin should have their serum electrolytes and renal function (BUN and/or serum creatinine) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION section in the complete prescribing information.

Drug Interactions: Potassium-depleting *corticosteroids* and *diuretics* may be major contributing factors to digitalis toxicity. *Calcium*, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. *Quinidine*, *verapamil*, and *amiodarone* cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. Certain *antibiotics* increase digoxin absorption in patients who inactivate digoxin by bacterial metabolism in the lower intestine, so that digitalis intoxication may result. *Propantheline* and *diphenoxylate*, by decreasing gut motility, may increase digoxin absorption. *Antacids*, *kaolin-pectin*, *sulfasalazine*, *neomycin*, *cholestyramine* and certain *anticancer drugs* may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. There have been inconsistent reports regarding the effects of other drugs on the serum digoxin concentration. *Thyroid* administration to a digitalized hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and *sympathomimetics* increases the risk of cardiac arrhythmias because both enhance ectopic pacemaker activity. *Succinylcholine* may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although ß adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Due to the considerable variability of these interactions, digoxin dosage should be carefully individualized when patients receive coadministered medications.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies performed in animals to evaluate carcinogenic potential.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated daily dose to a nursing infant will be far below the usual infant maintenance dose. Therefore, this amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when digoxin is administered to a nursing woman.

ADVERSE REACTIONS: The frequency and severity of adverse reactions to digoxin depend on the dose and route of administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS section). The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% of them being considered serious (one to four percent of patients receiving digoxin). Evidence suggests that the incidence of toxicity has decreased since the introduction of the serum digoxin assay and improved standardization of digoxin tablets. Cardiac toxicity accounts for about one-half, gastrointestinal disturbances for about one-fourth, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults:

Cardiac—Unifocal or multiform ventricular premature contractions, especially in bigeminal or trigeminal patterns, are the most common arrhythmias associated with digoxin toxicity in adults with heart disease.

Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional (nodal) rhythm and atrial tachycardia with block are also common arrhythmias caused by digoxin overdosage.

Excessive slowing of the pulse is a clinical sign of digoxin overdosage. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances. Digoxin may also induce other changes in the ECG (e.g. PR prolongation, ST depression), which represent digoxin effect and may or may not be associated with digitalis toxicity.

Gastrointestinal—Anorexia, nausea, vomiting and less commonly diarrhea are common early symptoms of overdosage. However, uncontrolled heart failure may also produce such symptoms. Digitalis toxicity very rarely may cause abdominal pain and hemorrhagic necrosis of the intestines.

CNS—Visual disturbances (blurred or yellow vision), headache, weakness, apathy and psychosis can occur.

Other—Gynecomastia is occasionally observed.

Infants and Children: Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more reliable signs of toxicity. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE:

Adults: Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear only near the expected time for maximum effect of the drug.

Potassium salts are commonly used, particularly if hypokalemia is present. Potassium chloride in divided oral doses totaling 3 to 6 grams of the salt (40 to 80 mEq K+) for adults may be given provided renal function is adequate (see below for potassium recommendations in Infants and Children).

When correction of the arrhythmia is urgent and the serum potassium concentration is low or normal, potassium should be administered intravenously in 5% dextrose injection. For adults, a total of 40 to 80 mEq (diluted to a concentration of 40 mEq per 500 ml) may be given at a rate not exceeding 20 mEq per hour, or slower if limited by pain due to local irritation. Additional amounts may be given if the arrhythmia is uncontrolled and potassium well-tolerated. ECG monitoring should be performed to watch for any evidence of potassium toxicity (e.g. peaking of T waves) and to observe the effect on the arrhythmia. The infusion may be stopped when the desired effect is achieved.

Note: Potassium should not be used and may be dangerous in heart block due to digoxin, unless primarily related to supraventricular tachycardia.

Other agents that have been used for the treatment of digoxin intoxication include lidocaine, procainamide, propranolol and phenytoin, although use of the latter must be considered experimental. In advanced heart block, temporary ventricular pacing may be beneficial. Digoxin Immune Fab (Ovine), Digibind®, can be used to reverse potentially life-threatening digoxin (or digitoxin) intoxication. Improvement in signs and symptoms of digitalis toxicity usually begins within ½ hour of Digibind administration. Each 40 mg vial of Digibind will neutralize 0.6 mg of digoxin (which is a usual body store of an adequately digitalized 70 kg patient).

Infants and Children: See Adult section for general recommendations for the treatment of arrhythmias produced by overdosage and for cautions regarding the use of potassium.

If a potassium preparation is used to treat toxicity, it may be given orally in divided doses totaling 1 to 1.5 mEq K+ per kilogram (kg) body weight (1 gram of potassium chloride contains 13.4 mEq K+).

When correction of the arrhythmia with potassium is urgent, approximately 0.5 mEq/kg of potassium per hour may be given intravenously, with careful ECG monitoring. The intravenous solution of potassium should be dilute enough to avoid local irritation; however, especially in infants, care must be taken to avoid intravenous fluid overload.

DOSAGE AND ADMINISTRATION: Recommended dosages are average values that may require considerable modification because of individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended doses.

In deciding the dose of digoxin, several factors must be considered:

1. The disease being treated. Atrial arrhythmias may require larger doses than heart failure.
2. The body weight of the patient. Doses should be calculated based upon lean or ideal body weight.
3. The patient's renal function, preferably evaluated on the basis of creatinine clearance.
4. Age is an important factor in infants and children.
5. Concomitant disease states, drugs or other factors likely to alter the expected clinical response to digoxin (see PRECAUTIONS and Drug Interactions sections).

Consult complete product information before prescribing.

IN THE EARLY TREATMENT OF CHF

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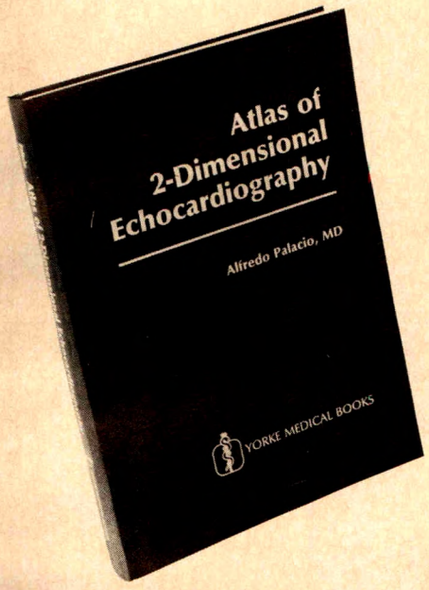

A "how-to-do-it" text/atlas presenting the broadest range of normal and abnormal 2-dimensional echocardiograms

Atlas of 2-Dimensional Echocardiography

by Alfredo Palacio, MD
Director of National Institute of Cardiology, Guayaquil, Ecuador
Foreword by David H. Spodick, MD, DSc
Professor of Medicine, University of Massachusetts Medical School; Director, Division of Cardiology, St. Vincent Hospital, Worcester, Massachusetts

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2-dimensional echocardiography complemented by M-mode echocardiography has become one of the most common noninvasive diagnostic tools used by the cardiologist. With publication of the ATLAS OF 2-DIMENSIONAL ECHOCARDIOGRAPHY, neophyte and expert alike now have available to them the most truly usable didactic presentation of the subject ever published.

A true atlas, this book provides in a **large 8¼ × 12 format 251 black and white half tones, 152 line drawings and 6 charts** which illustrate in exacting detail how to perform and interpret 2-dimensional echocardiograms on patients with existing and/or suspected heart disease. The lucid accompanying text leads the reader step-by-step through the entire process, leaving little to the imagination. It presents in the most simple, direct way possible the broadest range of normal and abnormal 2-dimensional echocardiograms. The descriptions and detailed illustrations in its technical sections will ensure the superior level of performance of echocardiographic techniques that is a sine qua non for good results.

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530 Factors of Importance for Prognosis in Men with Angina Pectoris Derived from a Random Population Sample. The Multifactor Primary Prevention Trial, Gothenburg, Sweden

Marianne Hagman, Lars Wilhelmsen, Kjell Pennert, and Hans Wedel

A random population sample of middle-aged men (n = 6,038) was followed for 11.3 years from a first screening. Men with uncomplicated angina pectoris (AP) had an incidence of fatal and nonfatal coronary artery disease (CAD) events 3 times higher than that of men without AP or myocardial infarction. Men with myocardial infarction with or without AP had an incidence of CAD events 7 to 8 times higher than that of men without AP or myocardial infarction. Similar differences were found for new cases of uncomplicated AP and myocardial infarction detected at a second screening carried out 4 years later and followed for 7.3 years. Elevated serum cholesterol, elevated blood pressure, smoking and angina attack score were independently associated with CAD endpoints during follow-up, with the increase in risk proving to be similar to the general population.

536 Assessment of Mitral Flow Velocity with Exercise by an Index of Stress-Induced Left Ventricular Ischemia in Coronary Artery Disease

George D. Mitchell, Richard C. Brunken, Markus Schwaiger, Bryan C. Donohue, Janine Krivokapich, and John S. Child

Exercise-induced myocardial ischemia results in both diastolic and systolic left ventricular (LV) dysfunction. To investigate the utility of Doppler assessment of LV diastolic function with exercise, 28 consecutive patients underwent digital stress echocardiography, measurement of mitral flow velocity by pulsed-wave Doppler and simultaneous stress thallium imaging. The percent increase in mean mitral flow velocity among controls was 101 ± 59 (n = 10), compared with 33 ± 24% in patients with stress-induced ischemia as evidenced by either exercise-induced wall-motion abnormalities by 2-dimensional echocardiography or perfusion defects by stress thallium imaging ($p < 0.005$). An increase in mean mitral flow velocity with exercise of >50% correctly identified 9 of 10 nonischemic control patients. An increase in mean mitral flow velocity of <50% predicted ischemia in 15 of 18 patients with evidence of stress-induced ischemia ($p < 0.005$). Thus, Doppler assessment of LV diastolic function with exercise expressed as the change in mean velocity of mitral flow is a useful indicator of stress-induced ischemia.

Continued on page A30

TONOCARD®
(TOCAINIDE HCl|MSD)

INDICATIONS AND USAGE

TONOCARD is indicated for the treatment of life-threatening ventricular arrhythmias.

TONOCARD is also indicated for the treatment of some patients with symptomatic ventricular arrhythmias.

Because TONOCARD has the potential to produce serious hematologic disorders (0.18 percent in clinical trials) particularly leukopenia or agranulocytosis (sometimes fatal), the use of TONOCARD should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks. (See WARNINGS.) For less serious arrhythmias alternative therapy with less severe toxicity, such as certain beta-blocking agents, should be considered.

Like all other antiarrhythmics, tocainide has not been shown to prevent sudden death in patients with serious ventricular ectopic activity, and also, like all other antiarrhythmics, it has potentially serious adverse effects, including the ability to worsen arrhythmias. It is therefore essential that each patient given tocainide be evaluated electrocardiographically and clinically prior to, and during, tocainide therapy to determine whether the response to tocainide supports continued treatment.

CONTRAINDICATIONS

Patients who are hypersensitive to this product or to local anesthetics of the amide type.

Patients with second- or third-degree atrioventricular block in the absence of an artificial ventricular pacemaker.

WARNINGS

Blood Dyscrasias: Agranulocytosis, bone marrow depression, leukopenia, neutropenia, hypoplastic anemia, thrombocytopenia and sequelae such as septicemia and septic shock have been reported in patients receiving TONOCARD. Most of these patients received TONOCARD within the recommended dosage range. Fatalities have occurred (with approximately 25 percent mortality in reported agranulocytosis cases). Since most of these events have been noted during the first 12 weeks of therapy, it is recommended that complete blood counts, including white cell, differential and platelet counts be performed, optimally, at weekly intervals for the first three months of therapy, and periodically thereafter. Complete blood counts should be performed promptly if the patient develops any signs of infection (such as fever, chills, sore throat, or stomatitis), bruising, or bleeding. If any of these hematologic disorders is identified, TONOCARD should be discontinued and appropriate treatment should be instituted if necessary. Blood counts usually return to normal within one month of discontinuation. Caution should be used in patients with pre-existing marrow failure or cytopenia of any type. (See ADVERSE REACTIONS.)

Acceleration of Ventricular Rate: Acceleration of ventricular rate occurs infrequently when antiarrhythmics are administered to patients with atrial flutter or fibrillation (see ADVERSE REACTIONS).

PRECAUTIONS

General

Pulmonary Fibrosis: Pulmonary fibrosis, interstitial pneumonitis, fibrosing alveolitis, pulmonary edema, and pneumonia, possibly drug related, have been reported in patients receiving TONOCARD. Many of these events occurred in patients who were seriously ill. The experiences are usually characterized by bilateral infiltrates on x-ray and are frequently associated with dyspnea and cough. Fever may or may not be present. Patients should be instructed to promptly report the development of any pulmonary symptoms such as exertional dyspnea, cough, or wheezing. Chest x-rays are advisable at that time. If these pulmonary disorders develop, TONOCARD should be discontinued. (See ADVERSE REACTIONS.)

In patients with known heart failure or minimal cardiac reserve, TONOCARD should be used with caution because of the potential for aggravating the degree of heart failure.

Caution should be used in the institution or continuation of antiarrhythmic therapy in the presence of signs of increasing depression of cardiac conductivity.

In patients with severe liver or kidney disease, the rate of drug elimination may be significantly decreased (see DOSAGE AND ADMINISTRATION).

Since antiarrhythmic drugs may be ineffective in patients with hypokalemia, the possibility of a potassium deficit should be explored and, if present, the deficit should be corrected.

Like all other oral antiarrhythmics, TONOCARD has been reported to increase arrhythmias in some patients (see ADVERSE REACTIONS).

Information for Patients

Patients should be instructed to promptly report the development of bruising or bleeding; any signs of infections such as fever, chills, sore throat, or soreness and ulcers in the mouth; any pulmonary symptoms, such as exertional dyspnea, cough, or wheezing; rash.

Laboratory Tests

As with other antiarrhythmics, abnormal liver function tests, particularly in the early stages of therapy, have been reported. Periodic monitoring of liver function should be considered. Hepatitis and jaundice have been reported in some patients.

Drug Interactions

Tocainide and lidocaine are pharmacodynamically similar. The concomitant use of these two agents may cause an increased incidence of adverse reactions, including central nervous system adverse reactions such as seizure.

Specific interaction studies with cimetidine, digoxin, metoprolol, and warfarin have been conducted; no clinically significant interaction was seen with cimetidine, digoxin, or warfarin; but tocainide and metoprolol had additive effects on wedge pressure and cardiac index. TONOCARD has also been used in open studies with digitalis, beta-blocking agents, other antiarrhythmic agents, anticoagulants, and diuretics without evidence of clinically significant interactions. Nevertheless, caution should be exercised in the use of multiple drug therapy.

Pregnancy

Pregnancy Category C. In a teratogenicity study in rabbits, tocainide was administered orally at doses of 25, 50, and 100 mg/kg/day (about 1 to 4 times the usual human dose). No evidence of a drug-related teratogenic effect was noted; however, these doses were maternotoxic and produced a dose-related increase in abortions and stillbirths. In a teratogenicity study in rats, an oral dose of 300 mg/kg/day (about 12 times the usual human dose) showed no evidence of treatment-related fetal malformations, but maternotoxicity and an increase in fetal resorptions were noted. An oral dose of 30 mg/kg/day (about twice the usual human dose) did not produce any adverse effects.

In reproduction studies in rats at maternotoxic oral doses of 200 and 300 mg/kg/day (about 8 and 12 times the usual human dose, respectively), dystocia, and delayed parturition occurred which was accompanied by an increase in stillbirths and decreased survival in offspring during the first week postpartum. Growth and viability of surviving offspring were not affected for the remainder of the lactation period.

There are no adequate and well-controlled studies in pregnant women. TONOCARD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether tocainide is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from TONOCARD, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

TONOCARD commonly produces minor, transient nervous system and gastrointestinal adverse reactions, but is otherwise generally well tolerated. TONOCARD has been evaluated in both short-term (n = 1,358) and long-term (n = 262) controlled studies as well as a compassionate use program. Dosages were lower in most of the controlled studies (1200 mg/day) and higher in the compassionate use program (1800 mg and more). In long-term (2-6 months) controlled studies, the most frequent adverse reactions were dizziness/vertigo (15.3 percent), nausea (14.5 percent), paresthesia (9.2 percent), and tremor (8.4 percent). These reactions were generally mild, transient, dose-related and reversible with a reduction in dosage, by

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taking the drug with food, or by therapy discontinuation. Tremor, when present, may be useful as a clinical indicator that the maximum dose is being approached. Adverse reactions leading to therapy discontinuation occurred in 21 percent of patients in long-term controlled trials and were usually related to the nervous system or digestive system.

Adverse reactions occurring in greater than one percent of patients from the short-term and long-term controlled studies appear in the following table:

	Percent of Patients Controlled Studies	
	Short-term (n = 1,358)	Long-term (n = 262)
BODY AS A WHOLE		
Tiredness/drowsiness/ fatigue/lethargy/ lassitude/ sleepiness	1.6	0.8
Hot/cold feelings	0.5	1.5
CARDIOVASCULAR		
Hypotension	3.4	2.7
Bradycardia	1.8	0.4
Palpitations	1.8	0.4
Chest pain	1.6	0.4
Conduction disorders	1.5	0.0
Left ventricular failure	1.4	0.0
DIGESTIVE		
Nausea	15.2	14.5
Vomiting	8.3	4.6
Anorexia	1.2	1.9
Diarrhea/loose stools	0.0	3.8
NERVOUS SYSTEM/PSYCHIATRIC		
Dizziness/vertigo	8.0	15.3
Paresthesia	3.5	9.2
Tremor	2.9	8.4
Confusion/ disorientation/ hallucinations	2.1	2.7
Headache	2.1	4.6
Nervousness	1.5	0.4
Altered mood/ awareness	1.5	3.4
Incoordination/ unsteadiness/ walking disturbances	1.2	0.0
Anxiety	1.1	1.5
Ataxia	0.2	3.0
SKIN		
Diaphoresis	5.1	2.3
Rash/skin lesion	0.4	8.4
SPECIAL SENSES		
Blurred vision/visual disturbances	1.3	1.5
Tinnitus/ hearing loss	0.4	1.5
Nystagmus	0.0	1.1

An additional group of about 2,000 patients has been treated in a program allowing for the use of TONOCARD under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy, and comparatively high doses of TONOCARD were used. Fifty-four percent of the patients continued in the program for one year or longer, and 12 percent were treated for longer than three years, with the longest duration of therapy being nine years. Adverse reactions leading to therapy discontinuation occurred in 12 percent of patients (usually central nervous system effects or rash). A tabulation of adverse reactions occurring in one percent or more of patients follows:

	Percent of Patients Compassionate Use (n = 1,927)
CARDIOVASCULAR	
Increased ventricular arrhythmias/PVCs	10.9
CHF/progression of CHF	4.0
Tachycardia	3.2
Hypotension	1.8
Conduction disorders	1.3
Bradycardia	1.0
DIGESTIVE	
Nausea	24.6
Anorexia	11.3
Vomiting	9.0
Diarrhea/loose stools	6.8
MUSCULOSKELETAL	
Arthritis/arthralgia	4.7
Myalgia	1.7
NERVOUS SYSTEM/PSYCHIATRIC	
Dizziness/vertigo	25.3
Tremor	21.6
Nervousness	11.5
Confusion/ disorientation/ hallucinations	11.2
Altered mood/ awareness	11.0
Ataxia	10.8
Paresthesia	9.2

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	Percent of Patients Compassionate Use (n = 1,927)
SKIN	
Rash/skin lesion	12.2
Diaphoresis	8.3
Lupus	1.6
SPECIAL SENSES	
Blurred vision/vision disturbances	10.0
Nystagmus	1.1

Adverse reactions occurring in less than one percent of patients in either the controlled studies or the compassionate use program or since the drug was marketed are as follows:

Body as a Whole: Septicemia; septic shock; syncope; vaso-vagal episodes; edema; fever; chills; cinchonism; asthenia; malaise.

Cardiovascular: Ventricular fibrillation; extension of acute myocardial infarction; cardiogenic shock; pulmonary embolism; angina; AV block; hypertension; claudication; increased QRS duration; pleurisy/pericarditis; prolonged QT interval; right bundle branch block; cardiomegaly; sinus arrest; vasculitis; orthostatic hypotension; cold extremities.

Digestive: Hepatitis, jaundice (see PRECAUTIONS), abnormal liver function tests; pancreatitis; abdominal pain/discomfort; constipation; dysphagia; gastrointestinal symptoms (including dyspepsia); stomatitis; dry mouth; thirst.

Hematologic: Agranulocytosis; bone marrow depression; hypoplastic anemia; hemolytic anemia; anemia; leukopenia; neutropenia; thrombocytopenia; eosinophilia.

Metabolic and Immune: Hypersensitivity Reaction (including some of the following symptoms or signs: rash, fever, joint pains, abnormal liver function tests, eosinophilia); increased ANA.

Musculoskeletal: Muscle cramps; muscle twitching/spasm; neck pain; pain radiating from neck; pressure on shoulder.

Nervous System/Psychiatric: Coma; convulsions/seizures; myasthenia gravis; depression; psychosis; psychic disturbances; agitation; decreased mental acuity; dysarthria; impaired memory; increased stuttering/slurred speech; insomnia/sleeping disturbances; local anesthesia; dream abnormalities.

Respiratory: Respiratory arrest; pulmonary edema; pulmonary fibrosis; fibrosing alveolitis; pneumonia; interstitial pneumonitis; dyspnea; hiccough; yawning.

Skin: Stevens-Johnson syndrome; exfoliative dermatitis; erythema multiforme; urticaria; alopecia; pruritus; pallor/flushed face.

Special Senses: Diplopia; earache; taste perversion/smell perversion.

Urogenital: Urinary retention; polyuria/increased diuresis.

Agranulocytosis, bone marrow depression, leukopenia, neutropenia, hypoplastic anemia, and thrombocytopenia have been reported (0.18 percent) in patients receiving TONOCARD in controlled trials and the compassionate use program. Most of these events have been noted during the first 12 weeks of therapy. (See WARNINGS.)

Pulmonary fibrosis, interstitial pneumonitis, fibrosing alveolitis, pulmonary edema, and pneumonia, possibly drug related, have been reported in patients receiving TONOCARD. The incidence of pulmonary fibrosis (including interstitial pneumonitis and fibrosing alveolitis) was 0.11 percent in controlled trials and the compassionate use program. These events usually occurred in seriously ill patients. Symptoms of these pulmonary disorders and/or x-ray changes usually occurred following 3-18 weeks of therapy and two patients died. (See PRECAUTIONS.)

A number of disorders, in which a causal relationship with TONOCARD has not been established, have been reported in seriously ill patients. These include: renal failure, renal dysfunction, myocardial infarction, cerebrovascular accidents, and transient ischemic attacks. These disorders may be related to the patient's underlying condition.

HOW SUPPLIED

Scored tablets containing 400 mg or 600 mg in bottles of 100 and unit-dose packages of 100.

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541 Dynamics of Early and Late Left Ventricular Filling Determined by Doppler Two-Dimensional Echocardiography During Percutaneous Transluminal Coronary Angioplasty

Leigh K. Bowman, Michael W. Cleman, Henry S. Cabin, Barry L. Zaret, and C. Carl Jaffe

Doppler 2-dimensional echocardiography was used to measure ventricular filling during percutaneous transluminal coronary angioplasty (PTCA). During left anterior descending artery PTCA there was a 35% decrease in early peak filling rate from 269 ± 88 to 169 ± 55 ml/s ($p < 0.0005$). In circumflex or dominant right coronary artery PTCA the early peak filling rate decreased 15% from 325 ± 126 to 248 ± 137 ml/s ($p < 0.005$). Rather than an expected increase in atrial stroke volume and a decrease in early to late filling ratio during coronary occlusion, there was a 28% decrease in atrial stroke volume during left anterior descending coronary artery PTCA and a 6% decrease during right coronary and circumflex PTCA. Because of the decrease in both early and late ventricular filling, peak early to late filling ratio showed only a small change during PTCA. Global systolic function measured on subsequent inflations during PTCA using 2-dimensional echocardiography showed ejection fraction decreased from 62 ± 6% to 35 ± 7% ($p < 0.0005$) during left anterior descending coronary artery PTCA and correlated highly with the mean percent decrease in early peak filling rate ($r = 0.95$). We conclude that during acute ischemia there are marked abnormalities in both early and late ventricular filling that are paralleled by a commensurate decrease in systolic function. There is also a decrease in atrial stroke volume during coronary occlusion that may be due to atrial pump failure induced by atrial afterload mismatch.

546 Early and Late Assessment of Stenosis Geometry After Coronary Arterial Stenting

Jacques Puel, Yves Juilliere, Michel E. Bertrand, Anthony F. Rickards, Ulrich Sigwart, and Patrick W. Serruys

This study assessed early and late modifications in stenosis geometry after stenting of coronary arteries. Quantitative coronary angiography was performed in 11 patients (mean age 55 years) with single coronary artery stenosis. Immediately following stent implantation, an additional increase in minimal luminal cross-sectional area of the dilated vessel was observed, suggesting that the self-expanding stainless-steel endoprosthesis used in this study had a dilating function. After a 3-month follow-up, neointimal poliferation was the likely cause of a small diffuse narrowing of the stented artery without hemodynamic repercussions. Whether this was a progressive process leading to important restenosis at long-term follow-up is unknown. Stenting of coronary arteries is a potentially valuable technique for preventing both abrupt closure and late restenosis.

Continued on page A34

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AND
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A beta$_1$-selective (cardioselective) blocking agent.

DESCRIPTION: TENORMIN (atenolol), a synthetic, beta$_1$-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2′-hydroxy-3′-[(1 methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C).

TENORMIN is available as 50 mg and 100 mg tablets for oral administration.

Inactive Ingredients: magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN should be withdrawn. (See Dosage and Administration.)

Cessation of Therapy With TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with other beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. To date, there has been no report of myocardial infarction or severe angina upon withdrawal of TENORMIN, probably due to its long plasma half-life. Because of the problems encountered with other beta blockers, when discontinuation of TENORMIN is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinstituted, at least temporarily. (See Dosage and Administration.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg, and a beta$_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see section on Overdosage). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See Dosage and Administration.)

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (See Dosage and Administration.)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose), and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN (atenolol) and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the US studies (volunteered side effects) and then from both US and foreign studies (volunteered and elicited side effects):

US STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), lightheadedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS US AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), lightheadedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

HEMATOLOGIC: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

ALLERGIC: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

CENTRAL NERVOUS SYSTEM: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

GASTROINTESTINAL: Mesenteric arterial thrombosis, ischemic colitis.

OTHER: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

MISCELLANEOUS: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

BRADYCARDIA: Atropine or another anticholinergic drug.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CONGESTIVE HEART FAILURE: Conventional therapy.

HYPOTENSION (DEPENDING ON ASSOCIATED FACTORS): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

BRONCHOSPASM: Aminophylline, isoproterenol, or atropine.

HYPOGLYCEMIA: Intravenous glucose.

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within 1 to 2 weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within 1 week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four hour control with once-daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once-a-day oral doses of 200 mg.

Patients with Renal Impairment: Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73 m2 (normal range is 100-150 mL/min/1.73 m2); therefore, the following maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (mL/min/1.73 m2)	Atenolol Elimination Half-life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually over a period of about 2 weeks. Patients should be carefully observed and advised to limit physical activity to a minimum.

HOW SUPPLIED: Tablets of 50 mg atenolol, NDC 0310-0105 (round, flat, uncoated white tablets identified with ICI debossed on one side and 105 debossed on the other side, bisected) are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Tablets of 100 mg atenolol, NDC 0310-0101 (round, flat, uncoated white tablets identified with ICI debossed on one side and 101 debossed on the other side) are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

Protect from heat, light, and moisture.

A/11/86

*Cardioselectivity denotes a relative preference for β_1-receptors, located chiefly in cardiac tissue. This preference is not absolute.

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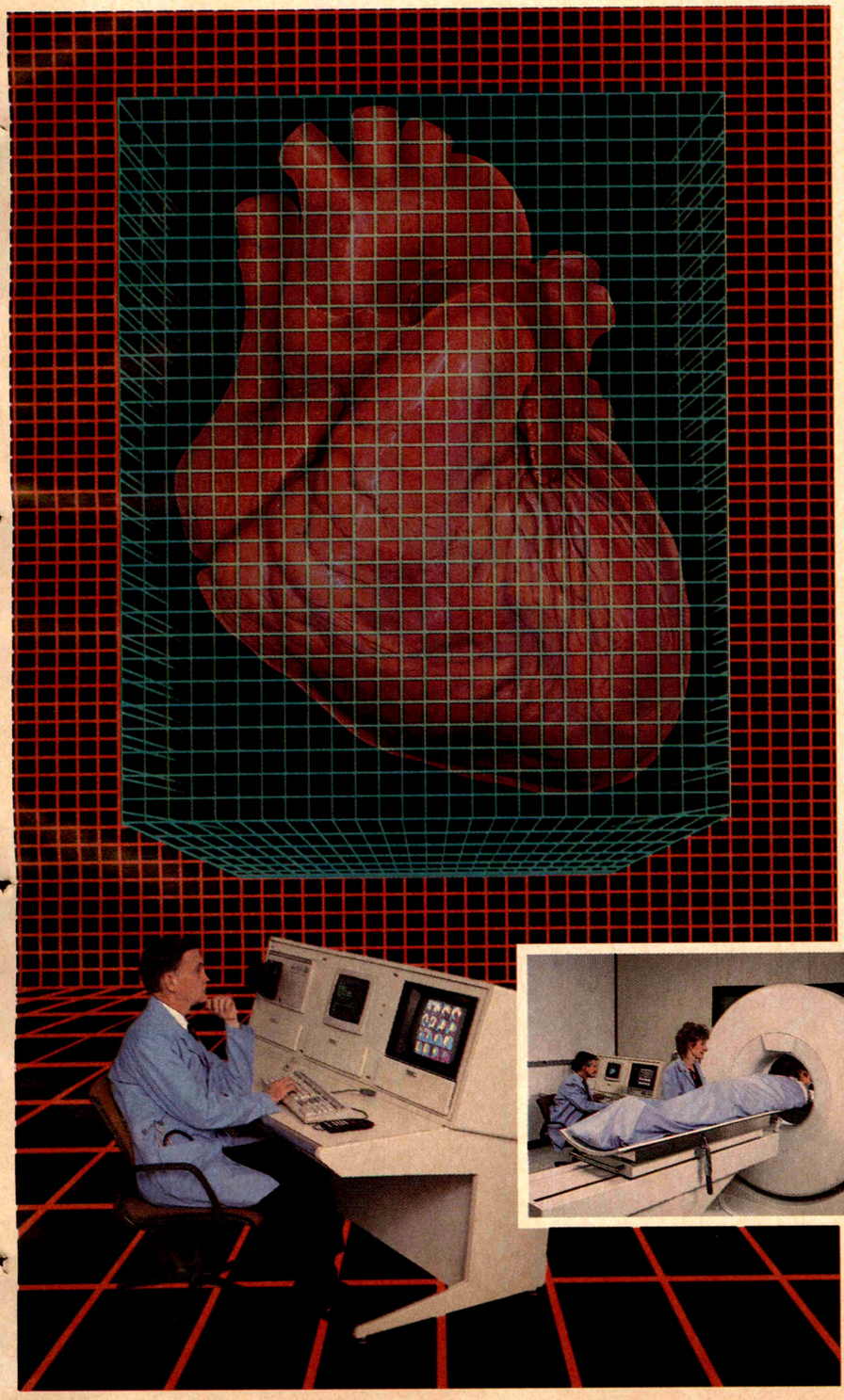

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A33

554 Intraaortic Balloon Pumping for Prolonged Circulatory Support

Paul S. Freed, Tarik Wasfie, Barina Zado, and Adrian Kantrowitz

Of 733 patients who received an intraaortic balloon pump between 1967 and 1982, 27 were supported for 20 days or more (range 20 to 71 days). Complications, including vascular compromise (37%), infections (67%) and bleeding (26%), were significantly more frequent in the prolonged-support patient than in those assisted <20 days (15%, $p = 0.001$; 25%, $p = 0.0001$; and 15%, $p = 0.04$, respectively). Survival rates of the 2 groups were similar: 63% in the prolonged-support group and 57% among controls ($p = 0.5$). Of 17 prolonged-support patients discharged from the hospital, 9 died within 6 months and 8 survived >2 years. No patient with chronic congestive heart failure ever became a long-term survivor. Prolonged intraaortic balloon pumping support in chronic congestive heart failure patients lacking surgically correctable lesions can extend life while arrangements for definitive therapy are made (transplant, permanent mechanical assistance). Where definitive therapy is unavailable, intraaortic balloon pumping may provide additional months of life.

558 Risks Associated With Intraaortic Balloon Pumping in Patients With and Without Diabetes Mellitus

Tarik Wasfie, Paul S. Freed, Melvyn Rubenfire, Waldemar Wajszczuk, Paula Reimann, Witold Brozyna, M. Anthony Schork, Jay Kozlowski, and Adrian Kantrowitz

Between 1967 and 1982, intraaortic balloon pumping (IABP) was attempted in 733 patients. Of those, 132 were diabetic: 51 patients were managed with diet alone, 46 took oral hypoglycemic agents and 35 patients needed insulin. Vascular complications associated with IABP occurred in 34% of the insulin-dependent diabetics, 18% of other diabetics and 14% of nondiabetics. Infectious complications were 37, 22 and 25%, respectively. Seventy-five diabetic patients (57%) were discharged alive from the hospital after balloon pumping, essentially the same proportion as among nondiabetic patients (58%). We conclude that although diabetics incur a higher complication rate, IABP is not contraindicated.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

563 QRS Morphology-Dependent Pharmacodynamics in Multiform Ventricular Ectopic Activity

Kenneth M. Kessler, Daneil McAuliffe, Patricia Kozlovskis, Richard G. Trohman, Liaqat Zaman, Agustin Castellanos, Rafael Sequeira, and Robert J. Myerburg

The effect of an infusion of intravenous procainamide on the frequency of ventricular premature complexes (VPCs) of differing QRS morphologies was studied in 20 patients with multiform ectopic activity. In 8 patients, VPCs of the most frequent QRS morphology remained suppressed at lower procainamide concentrations and for longer times than did VPCs of

Continued on page A45

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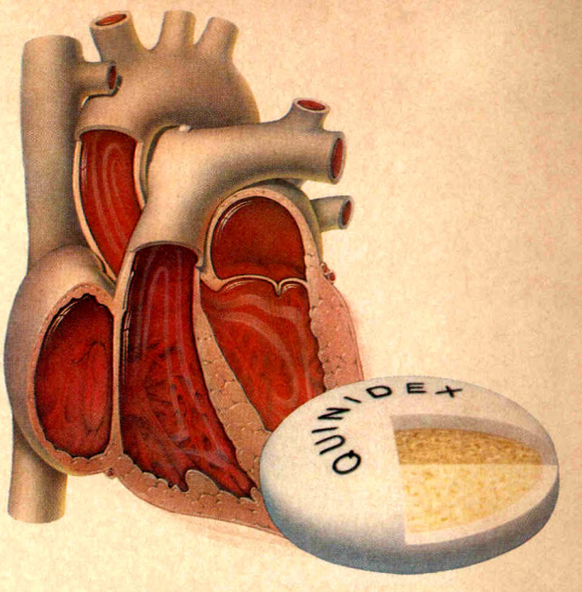

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Some patients may require t.i.d. dosing.

QUINIDEX EXTENTABS®

(Quinidine Sulfate, USP) 300mg

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Pharmaceutical Division, Richmond, Virginia 23261-6609

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Please see adjacent page for brief summary.

QUINIDEX
EXTENTABS®
(Quinidine Sulfate, USP)

The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4–8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	Effect
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Rev. June 1987

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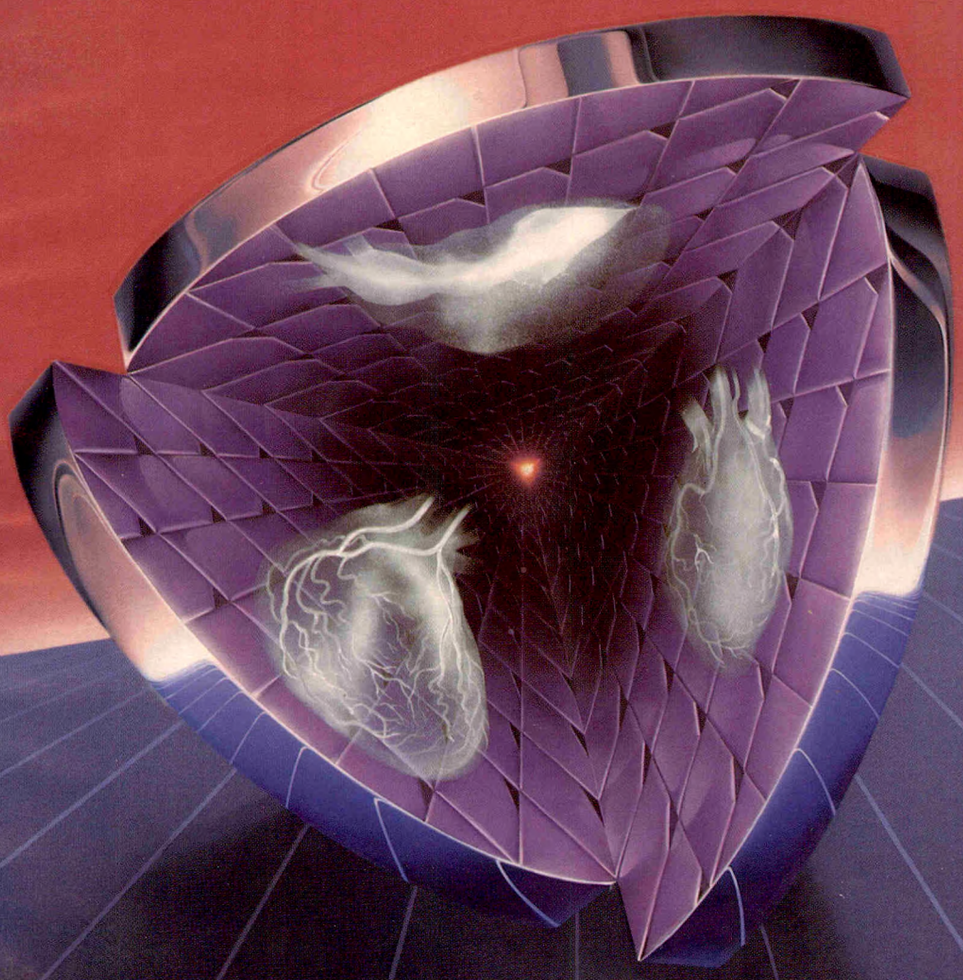

The image of safety in angiocardiography.

In angiocardiography, you ask a lot of the contrast agent you use.

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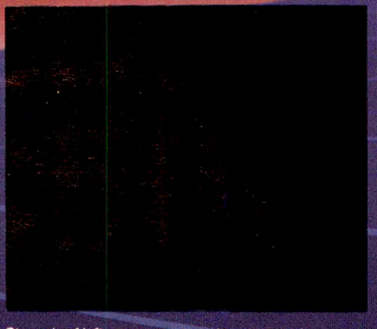
Experience with OMNIPAQUE in clinical use and trials continues to demonstrate its unique combination of lowest chemotoxicity and low osmolality, providing the best of all three.



Stenosis of left coronary artery demonstrated with OMNIPAQUE.

NONIONIC

OMNIPAQUE®

(IOHEXOL)

An ongoing record of safety in angiocardiography.

See next page for important product information concerning contraindications, warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations.

OMNIPAQUE® 240 300 350

INJECTION (IOHEXOL) INTRAVASCULAR

PLEASE CONSULT FULL PRODUCT INFORMATION BEFORE USING. A SUMMARY FOLLOWS:

DESCRIPTION: OMNIPAQUE is a nonionic, water-soluble radiographic contrast medium for intravascular administration in concentrations of 240, 300, and 350 mgI/mL. Each milliliter of iohexol solution contains 1.21 mg tromethamine and 0.1 mg edetate calcium disodium with the pH adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide, but it contains no preservatives.

CONTRAINDICATIONS: OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

WARNINGS: OMNIPAQUE should be used with extreme care in patients with severely impaired renal and/or hepatic function; severe thyrotoxicosis, hyperthyroidism, or an autonomously functioning thyroid nodule; diabetes with a serum creatinine level above 3 mg/dL. It is not recommended for use in patients with anuria.

Patients with known or suspected pheochromocytoma should receive a minimum of contrast medium if the benefit of the examination is judged to outweigh its risk; blood pressure should be monitored throughout the procedure, and measures for the treatment of hypertensive crisis should be readily available.

Contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly those with therapeutically resistant anuria. The combination of contrast agent and dehydration may precipitate myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over age 40, should be considered before instituting intravascular administration of contrast agents.

Ionic contrast media, when injected intravenously or intra-arterially, may promote sickling in individuals who are homozygous for sickle cell disease.

PRECAUTIONS: Diagnostic procedures that involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself. Competent personnel and emergency facilities should be available, since severe delayed reactions have been reported (see ADVERSE REACTIONS). The possibility of serious, life-threatening, fatal, anaphylactoid, or cardiovascular reactions should always be considered (see ADVERSE REACTIONS). It is of utmost importance that a course of action be carefully planned in advance for immediate treatment of serious reactions. Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with: advanced vascular disease, in diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease). *Patients should be well hydrated prior to and following iohexol administration.* Careful consideration of the potential risk of acute renal failure should be given before performing excretory urography in diabetic patients with diabetic nephropathy and in susceptible nondiabetic patients (often elderly with preexisting renal disease). Immediately following surgery, excretory urography should be used with caution in renal transplant recipients. The possibility of an idiosyncratic reaction in susceptible patients should always be considered (see ADVERSE REACTIONS). The susceptible population includes, but is not limited to, patients with a history of a previous reaction to contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity: bronchial asthma, hay fever, and food allergies. A thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast media, may be more accurate than pretesting in predicting potential adverse reactions.

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS). Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered and administered using separate syringes. Recent reports indicate that such pretreatment does not prevent serious, life-threatening reactions but may reduce both their incidence and severity.

Even though the osmolality of OMNIPAQUE is low compared to diatrizoate- or iothalamate-based ionic agents of comparable iodine concentration, the potential transitory increase in circulatory osmotic load in patients with congestive heart failure requires caution during injection. These patients should be observed for several hours following the procedure to detect delayed hemodynamic disturbances.

General anesthesia may be indicated in the performance of some procedures in selected adult patients; however, a higher incidence of adverse reactions has been reported in these patients and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of the anesthesia which can reduce cardiac output and increase the duration of exposure to the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria, because of the risk of inducing thrombosis and embolism.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be borne in mind during the catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

Selective coronary arteriography should be performed only in those patients in whom the expected benefits outweigh the potential risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

When OMNIPAQUE is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

The inhibitory effects of nonionic contrast media on mechanisms of hemostasis have been shown, in vitro, to be less than those of ionic contrast media at comparable concentrations. For this reason, standard angiographic procedures should always be followed: angiographic catheters should be flushed frequently, and prolonged contact of blood with contrast media in syringes and catheters should be avoided.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Parenteral products should be inspected and discarded if particulate matter or discoloration is present.

Drug/Laboratory Test Interaction: If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast medium administration. Thyroid function tests which do not depend on iodine estimation, eg, T_3 resin uptake or direct thyroxine assays, are not affected. Many radiopaque contrast agents are incompatible in vitro with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenesis, or whether OMNIPAQUE can affect fertility in men or women.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits with up to 100 times the recommended human dose. No evidence of impaired fertility or harm to the fetus has been demonstrated due to OMNIPAQUE. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known to what extent iohexol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Usually mild to moderate in severity. However, serious, life-threatening, and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media, including OMNIPAQUE. The injection of contrast media is frequently associated with the sensation of warmth and pain, especially in peripheral angiography; pain and warmth are less frequent and less severe with OMNIPAQUE than with many contrast media.

Cardiovascular System: Arrhythmias including PVCs and PACs (2%), angina/chest pain (1%), and hypotension (0.8%). Others including cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction were reported with an individual incidence of less than 0.4%. In controlled clinical trials involving 1,213 patients, one fatality occurred. A cause-and-effect relationship between this death and iohexol has not been established.

Nervous System: Vertigo [including dizziness and lightheadedness] (0.7%), pain (3%), photomas (2%), headache (2%), and taste perversion (1%). Others including anxiety, blurred vision, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis, and nystagmus were reported, with an individual incidence of less than 0.3%.

Respiratory System: Dyspnea and laryngitis, with an individual incidence of 0.1%.

Gastrointestinal System: Nausea (2%) and vomiting (0.6%). Others including diarrhea, dyspepsia, and dry mouth were reported, with an individual incidence of less than 0.2%.

Skin and Appendages: Urticaria (0.3%) and purpura (0.1%).

General Adverse Reactions to Contrast Media: The following reactions have been reported after administration of other intravascular iodinated contrast media, and rarely with iohexol. *Reactions due to technique:* hematomas and ecchymoses. *Hemodynamic reactions:* vein cramp and thrombophlebitis following intravenous injection. *Cardiovascular reactions:* rare cases of cardiac arrhythmias, reflex tachycardia, chest pain, cyanosis, hypertension, hypotension, peripheral vasodilatation, shock, and cardiac arrest. *Renal reactions:* occasionally, transient proteinuria; rarely, oliguria or anuria. *Allergic reactions:* asthmatic attacks, nasal and conjunctival symptoms, dermal reactions such as urticaria with or without pruritus, as well as pleomorphic rashes, sneezing, and lacrimation; rarely, anaphylactic reactions. Rare fatalities have occurred due to these or unknown causes. *Signs and symptoms related to the respiratory system:* pulmonary or laryngeal edema, bronchospasm, dyspnea; or *to the nervous system:* restlessness, tremors, convulsions. *Other reactions:* flushing, pain, warmth, metallic taste, nausea, vomiting, anxiety, headache, confusion, pallor, weakness, sweating, localized areas of edema (especially facial cramps), neutropenia, and dizziness. Rarely, immediate or delayed rigors can occur, sometimes accompanied by hyperpyrexia. Infrequently, "iodism" (salivary gland swelling) from organic iodinated compounds appears 2 days after exposure and subsides by the sixth day.

In general, the reactions that are known to occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Approximately 95% of adverse reactions accompanying the use of water-soluble intravascularly administered contrast agents are mild to moderate in degree. However, severe, life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred. Reported incidences of death range from 6.6 per 1 million (0.00066%) to 1 in 10,000 (0.01%). Most deaths occur during injection or 5 to 10 minutes later, the main feature being cardiac arrest, with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005%) patients.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast media, the dose, and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of dose injected, the speed of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that in the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Most adverse reactions to injectable contrast media appear within 1 to 3 minutes after the start of injection, but delayed reactions may occur.

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with angiocardiography than with other procedures. Cardiac decompensation, serious arrhythmias, angina pectoris, or myocardial ischemia or infarction may occur during angiocardiography and left ventriculography. Electrocardiographic and hemodynamic abnormalities occur less frequently with OMNIPAQUE than with diatrizoate meglumine and diatrizoate sodium injection.

OVERDOSAGE: Overdosage may occur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms include cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma, and cardiac arrest. Treatment of an overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

The intravenous LD_{50} values of OMNIPAQUE (in grams of iodine per kilogram body weight) are 24.2 in mice and 15.0 in rats.

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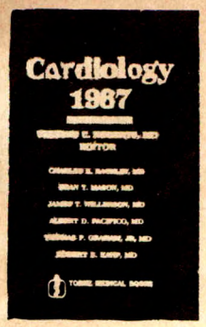

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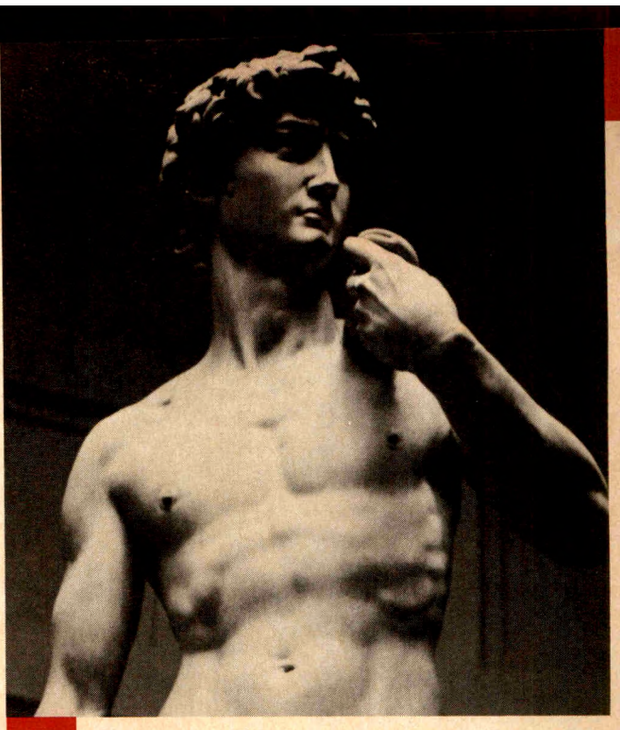

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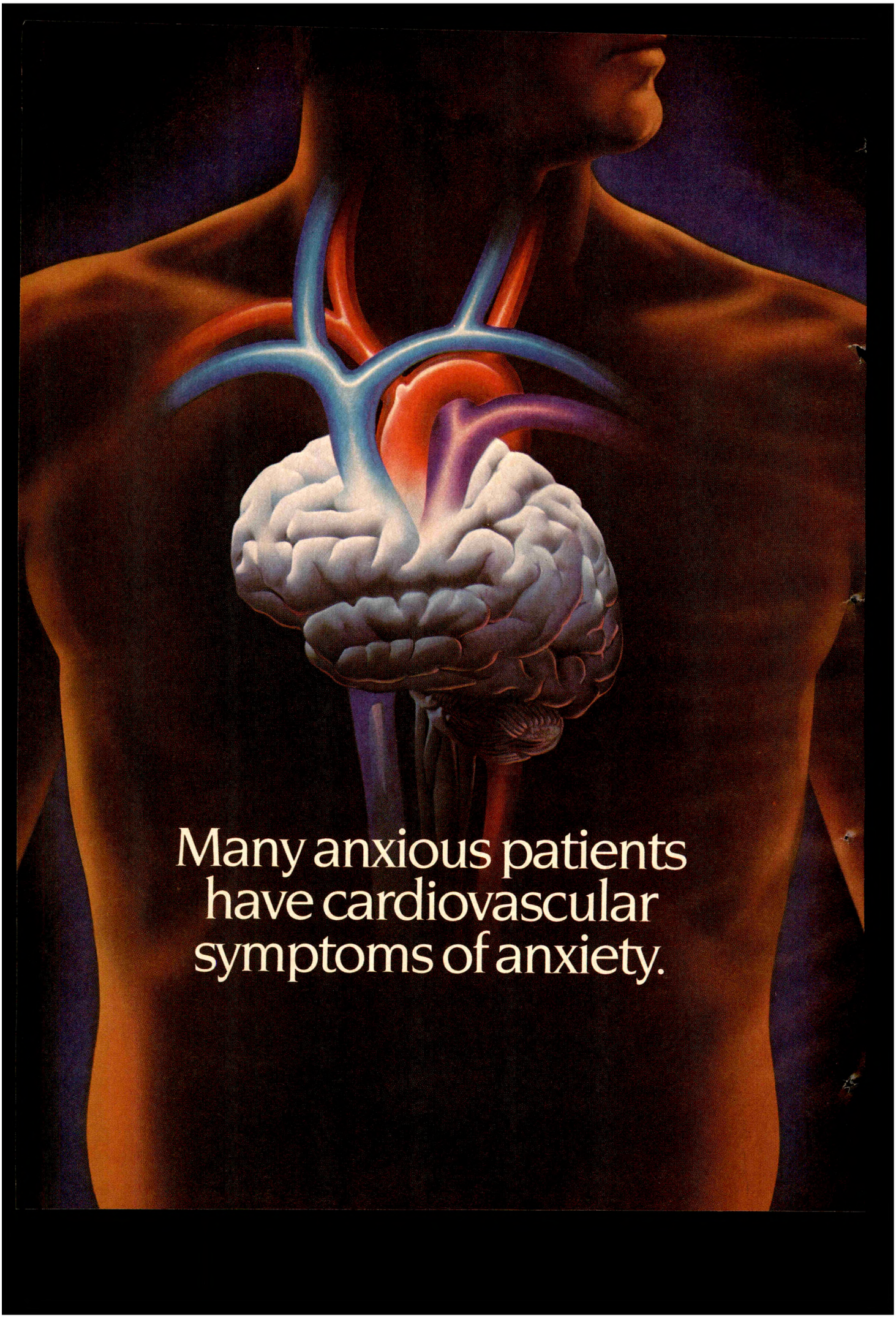
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have cardiovascular
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In double-blind, four-week clinical trials in 976 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.[1]

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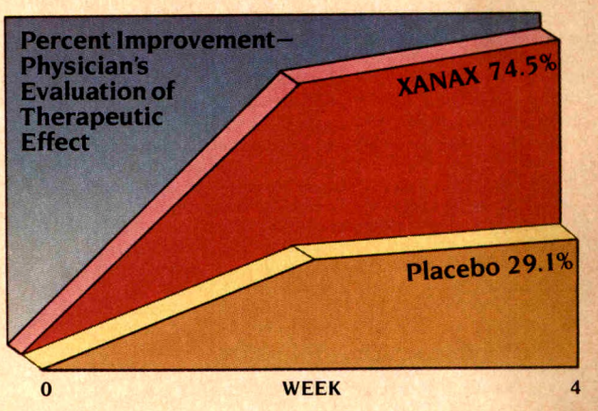

...including anxiety with associated cardiovascular symptoms...

Most patients in the study had cardiovascular symptoms even though cardiovascular disease was ruled out. XANAX was shown to effectively relieve anxiety with associated cardiovascular symptoms.

...and anxiety with associated depressive symptoms.

Over 70% of these patients experienced moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<0.014$) than placebo in improving depressed mood.

1. Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. *J Clin Psychiatry* 1981;42:347-351

Xanax® 0.5 mg Tablets

alprazolam C IV

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Please see adjacent page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with other drugs, e.g., cimetidine, have been reported. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures have been reported upon rapid decrease or abrupt discontinuation of XANAX. (See Precautions.)

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 milligram every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

Caution: Federal law prohibits dispensing without prescription. B-5-S

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Richard C. Brunken, MD *Assistant Professor of Radiology* Division of Nuclear Medicine and Biophysics The University of California School of Medicine at Los Angeles Los Angeles, California	**The Clinical Utility of Assessing Myocardial Metabolism with Positron Emission Tomography**
Robert M. Califf, MD *Assistant Professor of Medicine* Duke University Medical Center Durham, North Carolina	**The Use of t-PA in Acute Myocardial Infarction**
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the second most frequent QRS morphology (escape procainamide concentration = 2.8 ± 1.7 versus 5.4 ± 2.3 μg/ml, $p < 0.025$; time to escape, 244 ± 138 versus 98 ± 114 min; $p < 0.05$). In 9 other patients, VPCs of the second most frequent QRS morphology remained suppressed at lower procainamide concentrations and for longer times than did VPCs of the most frequent QRS morphology (escape procainamide concentration 2.9 ± 1.4 versus 8.3 ± 6.3 μg/ml, $p < 0.025$; time to escape 317 ± 114 versus 63 ± 80 min; $p < 0.001$). There is apparently a differential pharmacologic effect of procainamide on the foci or pathways responsible for the different QRS morphologies of multiform VPCs.

570 Tocainide Plus Quinidine for Treatment of Ventricular Arrhythmias

Jean T. Barbey, Katherine A. Thompson, Debra S. Echt, Raymond L. Woosley, and Dan M. Roden

Tocainide and quinidine were administered both as single agents and in combination to 14 patients with chronic ventricular arrhythmias. Therapy with tocainide was limited by the occurrence of dose-related adverse reactions in 8 patients, but could be titrated to a dose that was well tolerated in 13 of 14 and effective in 2 of 13. The addition of quinidine gluconate to the tolerated dose of tocainide increased the number of patients with arrhythmia suppression from 2 to 6. After tocainide washout, quinidine alone suppressed arrhythmias in only 3 patients. Analysis of electrocardiogram intervals showed that the drugs had additive effects on the coupling interval of the sinus beat to the predominant ectopic beat, but exerted antagonistic effects on the corrected QT interval. These findings suggest that the combination may be clinically useful, exerting pharmacologic effects unlike either agent alone.

574 Termination of Sustained Ventricular Tachycardia by External Noninvasive Pacing

Jerry C. Luck, Blair P. Grubb, Stephen E. Artman, Robert T. Steckbeck, and Michael L. Markel

Cardiac pacing is useful in the termination of sustained ventricular tachycardia (VT). External noninvasive temporary pacing was compared with endocardial burst ventricular pacing for the termination of sustained VT. External burst pacing terminated 14 of 16 VT morphologies (88%) when compared with endocardial burst termination. The average VT rate terminated by external burst pacing was 163 beats/min (range 125 to 200). These preliminary observations suggest that external burst pacing may be an effective means of terminating some sustained VTs.

578 Prognostic Significance of Arrhythmia Inducibility or Noninducibility at Initial Electrophysiologic Study in Survivors of Cardiac Arrest

Roger A. Freedman, Charles D. Swerdlow, Vivian Soderholm-Difatte, and Jay W. Mason

The value of arrhythmia inducibility or noninducibility at initial electrophysiologic study to predict the likelihood of arrhythmia recurrence was assessed in 150 consecutive survivors of cardiac arrest. Ventricular tachy-

cardia (≥6 beats) or ventricular fibrillation was induced in 113 patients (75%); ventricular arrhythmia was not induced in 37 patients (25%). During follow-up of a mean of 16 months (range 1 to 72), there were 65 arrhythmia recurrences (34 fatal) in 58 patients. Multivariate regression analysis showed that inducibility at initial study of ventricular tachycardia or ventricular fibrillation was an independent predictor of total arrhythmia recurrence ($p < 0.0001$) and fatal arrhythmia recurrence ($p = 0.02$). At 1 year, 25 ± 5% of patients with an inducible arrhythmia had a fatal arrhythmia recurrence compared with only 4 ± 4% of patients without ($p = 0.003$). Inducibility or noninducibility of ventricular arrhythmias at initial electrophysiologic study is a powerful, independent predictor of subsequent arrhythmia recurrence in survivors of cardiac arrest.

VALVULAR HEART DISEASE

583 Dual Balloon Technique for Valvuloplasty of Aortic Stenosis in Adults

Jeffrey M. Isner, Deeb N. Salem, Mark R. Desnoyers, Constance D. Fields, Kimberly R. Halaburka, Geralyn A. Slovenkai, Thomas J. Hougen, Eric J. Eichhorn, and Kenneth Rosenfield

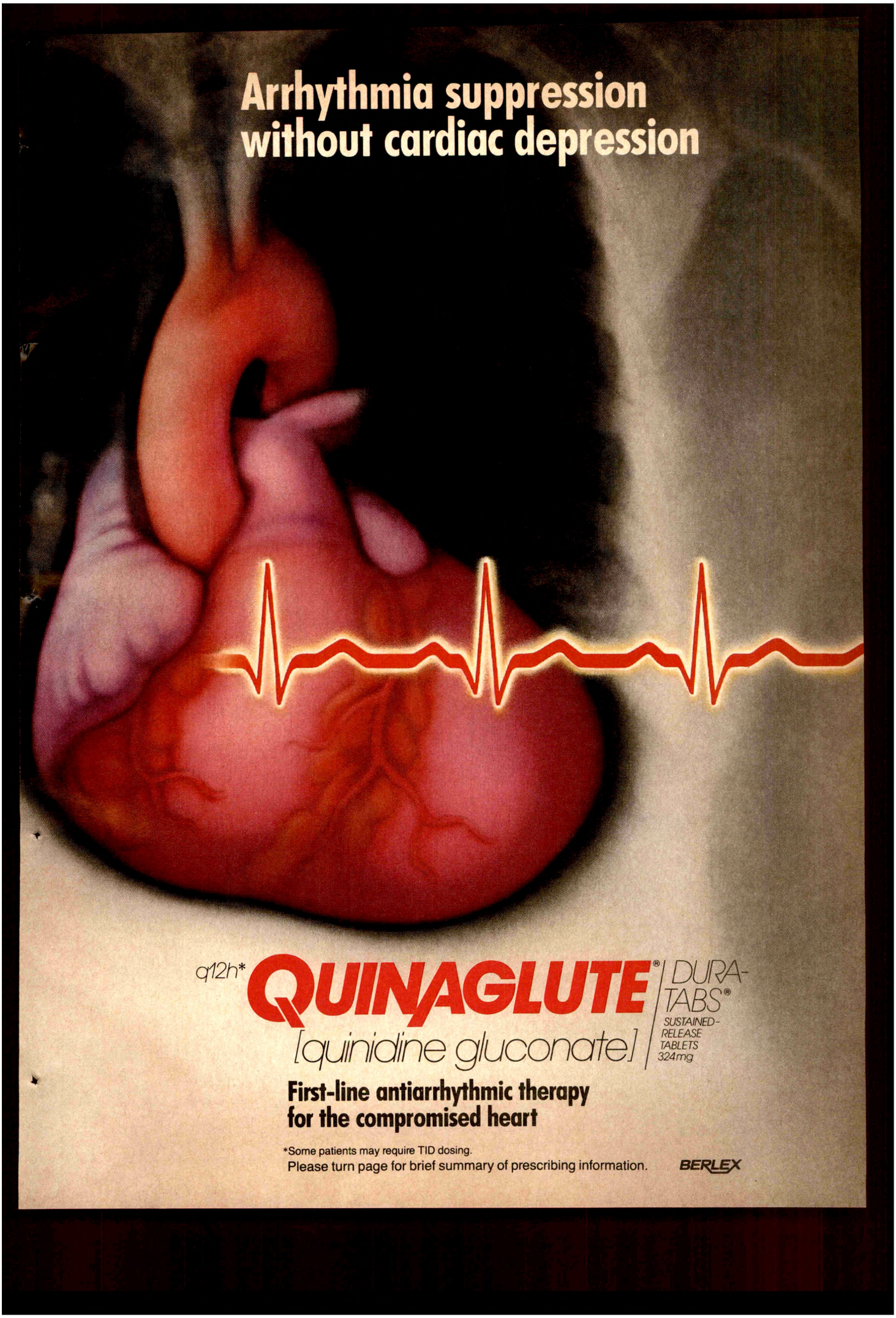
Because results obtained using the single balloon technique for aortic balloon valvuloplasty may occasionally be suboptimal, we used a dual balloon technique in a series of 16 patients in whom the results of the single balloon technique were judged to be suboptimal. Use of the dual balloon technique accomplished a further decrease in peak aortic valve gradient and further increase in calculated aortic valve area that were statistically significant when compared with the results obtained with the single balloon alone. No complications were observed that were directly attributable to the dual balloon technique. These preliminary results suggest that dual balloon valvuloplasty is efficacious and safe in selected patients with aortic stenosis.

590 Effect of Mitral Regurgitation on Diastolic Filling with Left Ventricular Hypertrophy

M. Abubakr Shaikh and Steven J. Lavine

Mitral regurgitation has been demonstrated to increase early left ventricular diastolic filling. The effect of mitral regurgitation on early diastolic filling in patients with abnormal diastolic function is not clearly understood. Using transmitral pulsed Doppler recordings, we studied 32 normal patients, 21 patients with left ventricular hypertrophy, 23 with left ventricular hypertrophy with mitral regurgitation and 15 with mitral regurgitation. Mitral regurgitation patients demonstrated increased early and late filling velocities. Patients with hypertrophy demonstrated reduced early filling velocities, increased late filling velocities and a redistribution of diastolic filling to atrial systole. Patients with hypertrophy and mitral regurgitation demonstrated increased early filling velocities, increased late filling velocities and a normal distribution of diastolic filling. The presence of mitral regurgitation normalizes early diastolic filling in patients with left ventricular hypertrophy. Caution should be exercised when using diastolic filling to evaluate diastolic function in patients with mitral regurgitation.

Continued on page A55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INDICATIONS AND USAGE: QUINAGLUTE® (quinidine gluconate) DURA-TABS® sustained-release tablets are indicated in the prevention and/or treatment of:

1. Ventricular arrhythmias: Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock). **2. Junctional (nodal) arrhythmias:** A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).

CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.

WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administation of quinidine.

2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered.

3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity.

7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4 to 8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.

Information for Patients: As with all solid oral medications, QUINAGLUTE® DURA-TABS® tablets should be taken with an adequate amount of fluid, preferably in an upright position, to facilitate swallowing.

Drug Interactions: *Drug*	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Potential for reduction of quinidine plasma levels
Quinidine with cimetidine	Potential for elevation of quinidine plasma levels
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. QUINAGLUTE® DURA-TABS® tablets should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers: Caution should be exercised when QUINAGLUTE® DURA-TABS® tablets are administered to a nursing woman due to passage of the drug into breast milk.

Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of QUINAGLUTE® DURA-TABS® tablets in children.

ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea.

Less frequently encountered adverse reactions:

Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.

Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.

Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.

Dermatologic: Rash, cutaneous flushing with intense pruritis, urticaria. Photosensitivity has also been reported.

Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although rare, there have been reports of lupus erythematosus in patients taking quinidine.

See package insert for full information. Rev. 11/85

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Preserves K^+ balance

Normalizes stress-induced systolic peaks with cardioselective beta-one blockade

Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

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metoprolol tartrate

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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent $beta_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a $beta_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and $beta_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.
Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.
Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.
Treatment
There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A $beta_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

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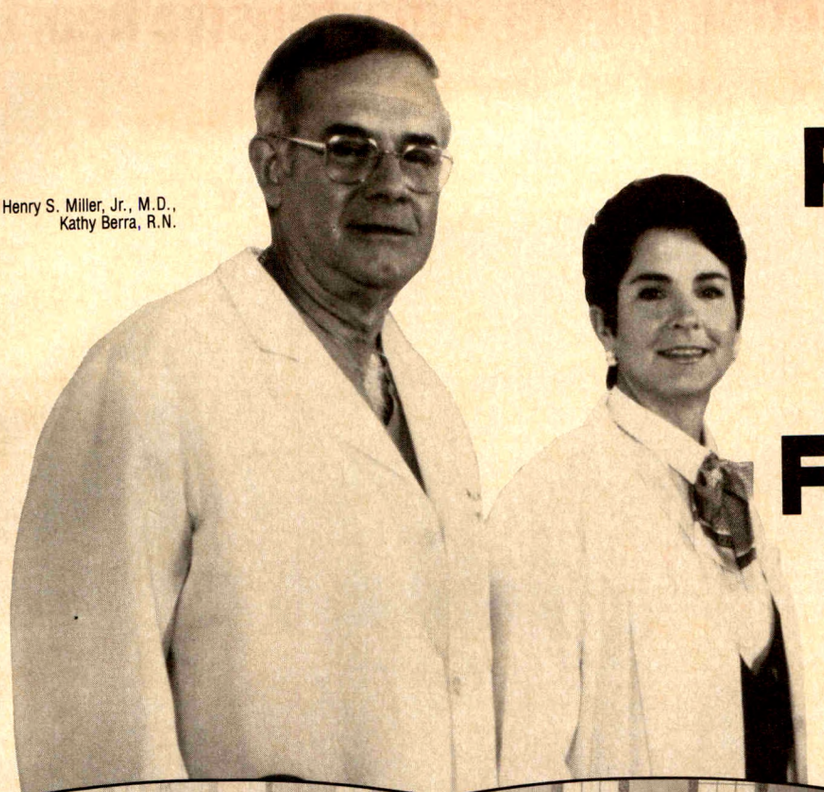

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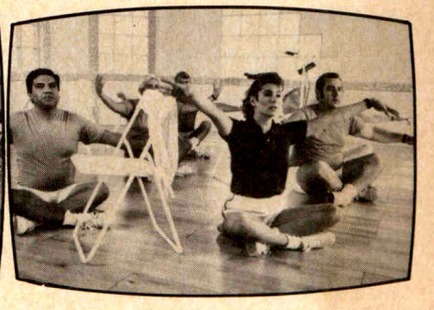

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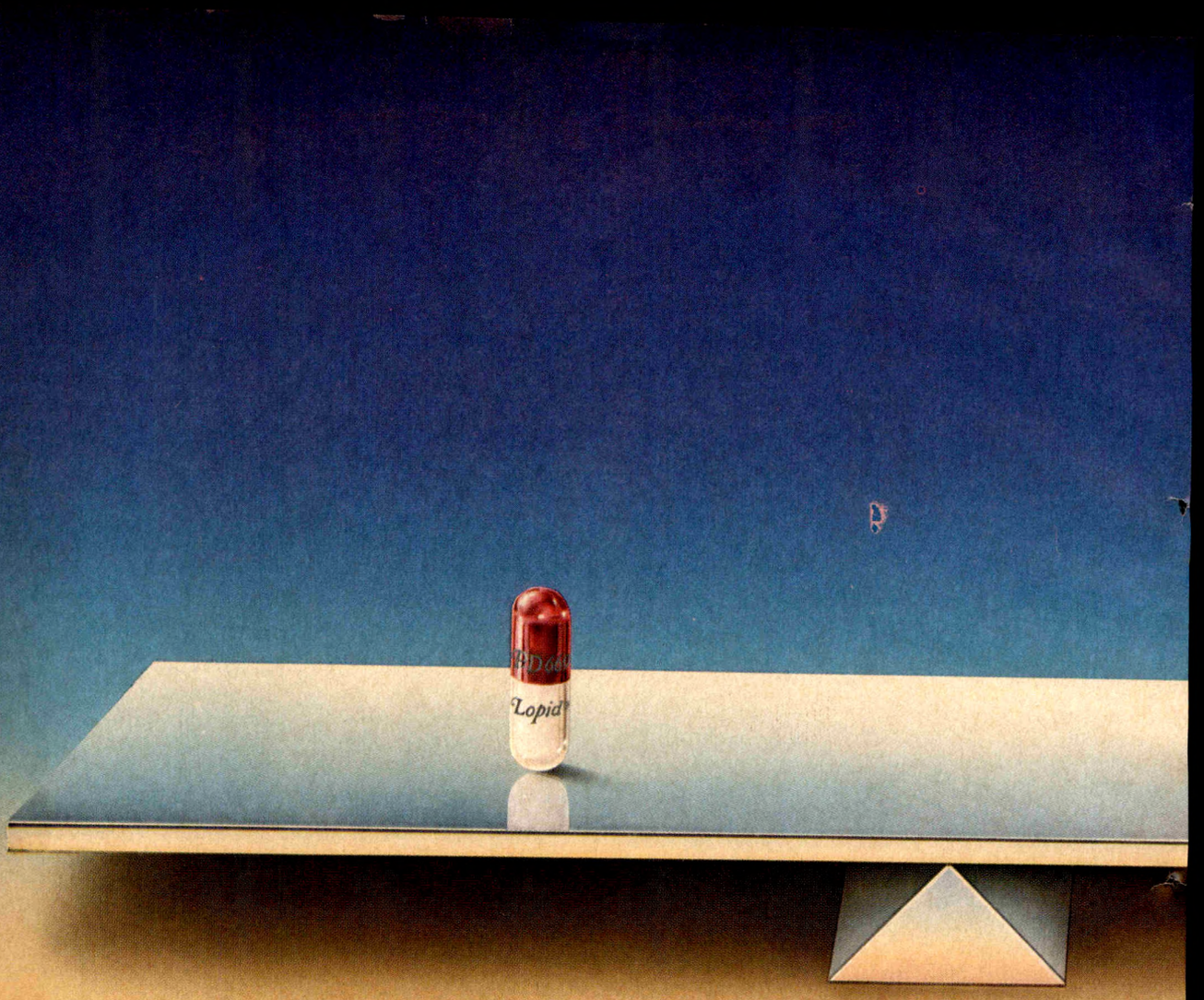

IN CERTAIN DYSLIPIDEMIAS

A Desirable Balance of Efficacy

LOPID® *300 mg*
(gemfibrozil capsules, USP)

Lopid is indicated for treatment of adult patients with very high serum triglyceride levels in hyperlipoproteinemia other than type I who present a risk of pancreatitis and who do not respond adequately to diet.

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with Patient Acceptance

Efficacy Lopid reduces synthesis[1-3] and increases clearance of triglyceride-rich VLDL.[2,3]

Patient acceptance Lopid has a very low order of side effects and has demonstrated limited effects on clinical and laboratory evaluations.[4]

Convenient BID dosage Two 300-mg capsules taken 30 minutes before morning and evening meals help ensure patient compliance.

Diet, exercise, and weight loss are the first choice in therapy of lipid disorders.

PARKE-DAVIS

Please see next page for references and a brief summary of prescribing information.

LOPID®
(gemfibrozil capsules, USP) 300 mg

Before prescribing, please see full prescribing information. A Brief Summary follows:

CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. It has been reported that LOPID may increase levels of high density lipoprotein (HDL) subfractions, HDL_2 and HDL_3 as well as apolipoproteins AI and AII. Epidemiological studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease. It is not yet known whether pharmacological interventions designed to raise HDL-cholesterol alter morbidity or mortality due to coronary heart disease.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID inhibits synthesis and increases clearance of VLDL carrier apolipoprotein B, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, mostly as the glucuronide conjugate, with less than 2% excreted as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO: HDL Cholesterol / Total Cholesterol
		Total	VLDL	LDL	HDL	
IIa	−44%	−4.2%	−44.3%	−5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	−6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. The initial treatment for hyperlipidemia is dietary therapy specific for the type of hyperlipoproteinemia. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV or type V hyperlipoproteinemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk. LOPID has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of gemfibrozil-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID (gemfibrozil capsules, USP) administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis—LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy**—Before instituting LOPID therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy**—Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Impairment of Fertility**—Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

4. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

5. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

6. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

7. **Liver Function**—Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

8. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria

Central Nervous System: headache, dizziness, blurred vision

Musculoskeletal: painful extremities

Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:

Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia

Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints, myositis

Central Nervous System: vertigo, insomnia, paresthesia, tinnitus

Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)

Miscellaneous: fatigue, malaise, syncope, alopecia

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

Caution—Federal law prohibits dispensing without prescription.

February 1987 0669G017

REFERENCES 1. Kashyap ML: The effect of gemfibrozil on plasma lipids and lipoproteins in man. *Vasc Med* 1984;1:16-21. 2. Kesäniemi YA, Grundy SM: Influence of gemfibrozil and clofibrate on metabolism of cholesterol and plasma triglycerides in man. *JAMA* 1984;251:2241-2246. 3. Brown MS, Goldstein JL: Drugs used in the treatment of hyperlipoproteinemias, in Gilman AG, Goodman LS, Rall TW, et al (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co, 1985, pp 827-845. 4. Lewis JE and the Multicenter Collaborative Study Group: Clinical use of gemfibrozil: A controlled multicenter trial. *Pract Cardiol* 1983;9(6):99-118.

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PD-56-JA-4300-P-1(4-87)

595 Noninvasive Assessment of Hemodynamic Responses to Exercise in Pulmonary Regurgitation After Operations to Correct Pulmonary Outflow Obstruction

Gerald R. Marx, Richard W. Hicks, Hugh D. Allen, and Stanley J. Goldberg

The purpose of this study was to determine the hemodynamic responses to exercise in postoperative patients with pulmonary regurgitation (PR) using Doppler-measured regurgitant fraction to indicate severity of disease. Maximal heart rate, oxygen consumption and workload capacity were measured during upright cycle ergometry. Cardiac output was measured at rest and during submaximal supine cycle ergometry by pulsed Doppler echocardiography. Oxygen consumption was simultaneously measured and exercise factor was calculated as the change in cardiac output per change in oxygen consumption. Twenty-seven patients were compared with 17 age-, size- and sex-matched control subjects. PR patients had larger right ventricles ($p \leq 0.001$); lower heart rate response ($p \leq 0.05$), lower maximal oxygen consumption ($p \leq 0.005$) and lower workloads ($p \leq 0.005$) during maximal exercise testing. Exercise factor was the same for both groups. Patients with mild PR had a normal response to exercise. However, patients with moderate and severe PR had lower maximal oxygen consumptions and maximal workloads compared with control subjects. Control, mild and moderate PR groups had similar exercise factors. Patients with severe PR and markedly low cardiac output responses. PR is associated with reduced exercise capability, which is related to disease severity.

602 Results of the Modified Fontan Operation in Adults

Richard A. Humes, Douglas D. Mair, Co-Burn J. Porter, Francisco J. Puga, Hartzell V. Schaff, and Gordon K. Danielson

The results of the modified Fontan operation in 77 patients 18 years of age and older indicated that the procedure can be performed with low mortality. The long-term outcome is favorable, but persistent ascites and edema may be a problem in some patients.

605 Effect of Iron Deficiency on Tissue Oxygen Delivery in Cyanotic Congenital Heart Disease

Samuel S. Gidding and James A. Stockman III

To test the hypothesis that tissue oxygen delivery would be affected by diminished iron stores in cyanotic congenital heart disease, serum ferritin, transferrin saturation, hemoglobin, red cell mean corpuscular volume (MCV), diphosphoglycerate (DPG), P50, blood gases, oxygen saturations and systemic oxygen transport were measured in 29 hypoxemic infants and children. When patients with P50 $\geq$30 mm Hg and P50 $<$30 mm Hg were compared, serum ferritin, transferrin saturation and MCV were significantly diminished in the high P50 group. Hemoglobin, aortic oxy-

gen saturation, PaO_2 and systemic oxygen transport were similar in both groups. In children with iron sufficiency, 15 of 21 had MCV >90th percentile for age and sex. Also, MCV >90th percentile has a positive predictive value of 0.88 for iron sufficiency. Thus, diminished iron stores are associated with a more right-shifted oxyhemoglobin dissociation curve (increased P50), and MCV >90th percentile is a marker for iron sufficiency in hypoxemic patients.

608 Surgical Risk Factors in Total Anomalous Pulmonary Venous Connection

Christopher R. Lincoln, Michael L. Rigby, Corrado Mercanti, Mohammad Al-Fagih, Michael C. Joseph, Graham A. Miller, and Elliott A. Shinebourne

Eighty-three patients underwent surgical correction of total anomalous pulmonary venous connection from 1973 to 1986. Diagnosis was established by cardiac catheterization and angiography in 56 patients, by clinical examination in 3, and by cross-sectional echocardiography alone in 24 of the last consecutive 28 patients. Pulmonary hypertension was present in 55% of those who underwent cardiac catheterization. Ten patients developed 1 or more pulmonary hypertensive crises during the early postoperative period. Analysis of risk factors for 30-day survival for all patients showed that the risk of early death was associated with the type of anomaly (infradiaphragmatic), occurrence of pulmonary hypertensive crises, year of operation, sex of the patient, and presence of preoperative heart failure. The 30-day hospital mortality from 1975 to the present is 8.5%.

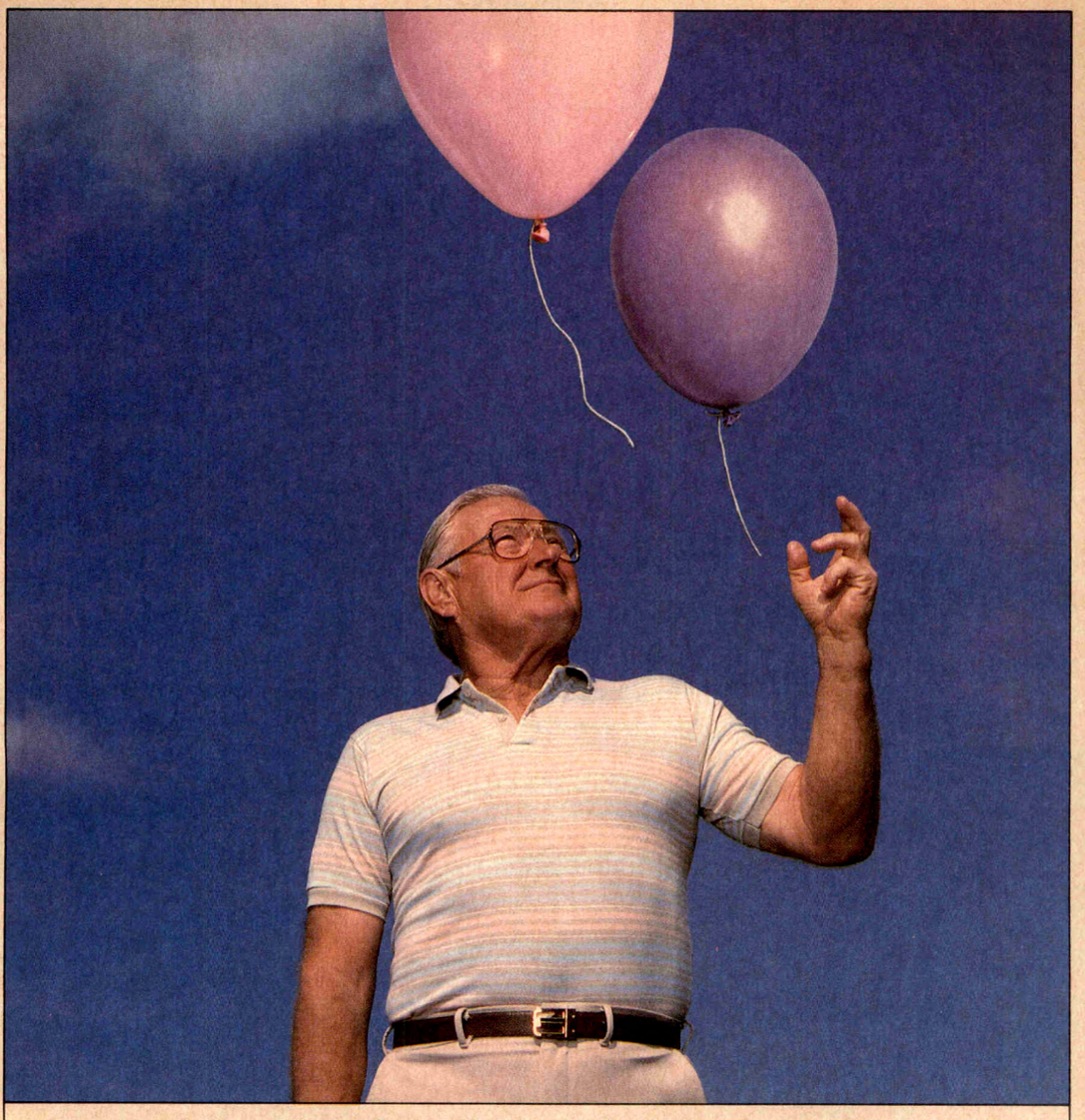
612 Accuracy of Electrical Impedance Cardiography for Measuring Cardiac Output in Children with Congenital Heart Defects

Daniel S. Miles, Robert W. Gotshall, Jane C. Golden, Dwight T. Tuuri, Robert H. Beekman III, and Terrence Dillon

The noninvasive technique of impedance cardiography was used to measure systemic blood flow (cardiac output) in children with congenital heart defects. Results were compared with values obtained for systemic blood flow measured by the direct Fick procedure. Patients evaluated consisted of a control group (n = 11) with no shunts, a group with intracardiac left-to-right shunting and an atrial septal defect (n = 7), another with a ventricular septal defect (n = 12), and an extracardiac left-to-right shunting with patent ductus arteriosus group (n = 7). The difference between systemic blood flow measured by the impedance or Fick techniques was ≤5% in each of the 4 groups. Impedance cardiography accurately measured systemic blood flow in children without shunts or valvular insufficiency. Likewise, systemic blood flow was accurately measured by impedance in the presence of intra- or extracardiac left-to-right shunting.

Continued on page A67

GENTLE RELEASE



Prescribe a slow and easy dual release mechanism when selecting a solid potassium supplement.

KLOTRIX® is the only slow-release KCl that employs a dual release mechanism: a wax matrix plus a patented permeable membrane coating.

for the patient who can't or won't drink liquid KCl

KLOTRIX®
(POTASSIUM CHLORIDE)

controlled-release tablets, 10 mEq

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(Please see Brief Summary of Prescribing Information on the following page)

KLOTRIX®
(POTASSIUM CHLORIDE)
CONTROLLED-RELEASE TABLETS, 10 mEq

DESCRIPTION: KLOTRIX is a film-coated (not enteric-coated) tablet containing 750 mg potassium chloride (equivalent to 10 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the GI tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with potassium-sparing diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. KLOTRIX is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years), cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. KLOTRIX should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS: Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram and clinical status of patient.

ADVERSE REACTIONS: Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose. One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION: The usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq per day or more for the treatment of potassium depletion.

Note: KLOTRIX® slow-release tablets must be swallowed whole and never crushed or chewed. Following release of the potassium chloride, the expended wax matrix, which is not absorbed, may be observed in the stool.

HOW SUPPLIED: Bottles of 100, 1000, and Unit Dose cartons of 100.

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CARDIOLOGIST/INTERNIST: BC/BE non-invasive Cardiologist to join two non-invasive and three invasive Cardiologists. The Durwood Medical Clinic, Charlotte, NC, is a 17 Physician Group Practice, representing all Sub-Specialties of Internal Medicine, and operating from three new offices. An outstanding opportunity to join a very busy Internal Medicine/Sub-Specialty/Referral practice, located in a growing metropolitan area. Position available August, 1988. Send CV to: J. F. Rice, Administrator, 125 Baldwin Ave., Charlotte, NC 28204.

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Call Mon–Fri, 9:00–5:00 (718) 522-1922
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CARDIOLOGIST—BC/BE sought to join a large hospital-based multi-specialty clinic. University affiliated residency program. Excellent fringe benefits. Competitive salary. California license required. Send CV to Aung-Win Chiong, MD, THE PERMANENTE MEDICAL GROUP, INC., P.O. Box 254999, Sacramento, CA 95865-4999, or call (916) 973-5748. An equal opportunity employer.

CARDIOLOGIST—A large Cardiology Practice in a major Northeastern City is seeking a well qualified Cardiologist to join an established growing Referral Practice. The Practice offers well rounded clinical, invasive and non-invasive opportunities, affiliation with a major Medical Center, and a large private Teaching Hospital. Please send letter and curriculum vitae to Box 695, The American Journal of Cardiology, 249 W. 17th St., New York, N.Y. 10011.

Cardiologist

LOVELACE

MEDICAL CENTER

Lovelace Medical Center, a 230-bed hospital located in Albuquerque, New Mexico, is seeking a **Cardiologist** to join a group of 4 Cardiologists. Our institution provides a full range of cardiovascular health care including an active cardiac catheterization lab which is involved in diagnostic catheterization as well as urgent and elective coronary angioplasty, valvuloplasty, and electrophysiologic studies. We also have an active cardiac surgery program and have a strong affiliation with the University of New Mexico training program for cardiology fellows.

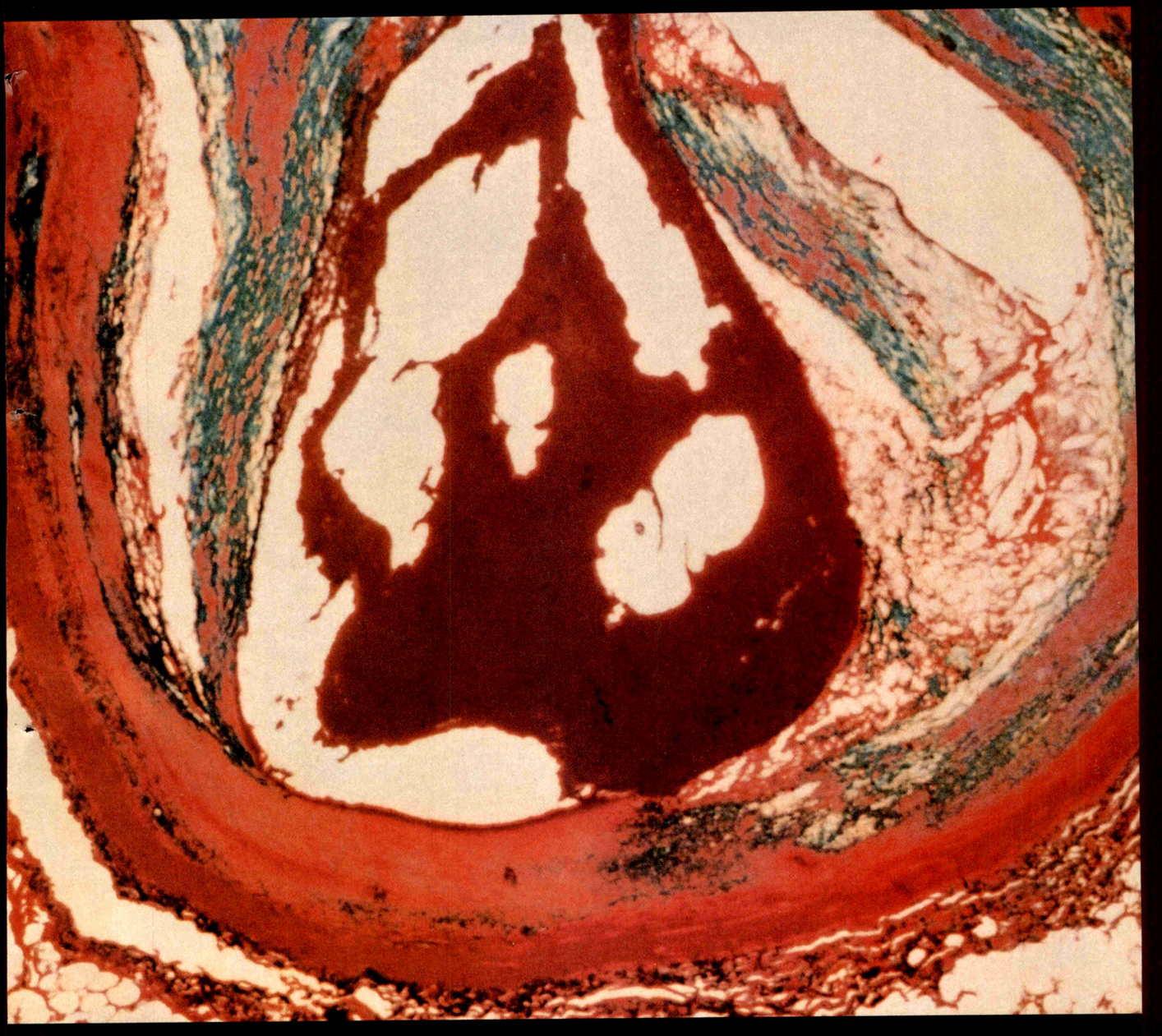
Lovelace Medical Center has opened a new hospital with an 8-bed Coronary Care Unit, a 2-bed open-heart recovery with an additional 10-bed Intensive Care Unit. State-of-the-art telemetry capabilities for arrhythmias detection are available in a step-down unit. The Cardiology Division also offers state-of-the-art echo and Doppler evaluations and the full range of cardiac nuclear studies.

The candidate we seek should be a fully trained cardiologist, specializing in noninvasive cardiology who is ABIM certified and board eligible or board certified in cardiology. Responsibilities will include supervising the noninvasive laboratory as well as the full range of clinical cardiovascular care and the education and training of Fellow within the Cardiology Department at the University of New Mexico. Attractive salary and benefits package is available. Please submit your curriculum vitae and letters of professional reference to: **Robert P. Croke, M.D. FACC, Chairman, Department of Cardiology, Lovelace Medical Center, 5400 Gibson Blvd SE, Albuquerque, NM 87108.**

Equal Opportunity Employer M/F/V/H

In the first critical hour of acute MI

MORTALITY REDUCED UP TO 47%



Cross section of a cardiac artery showing atheromatous plaque and occluding thrombus.

...and ventricular function improved.

Artist's interpretation of thrombolysis of a coronary artery occlusion.

Now...for acute MI

Intravenous

Streptase®

(Streptokinase)

Mortality reduced, ventricular function improved, unique benefits beyond lysis.

Lower in-hospital mortality with an acceptable level of risk[1]

- Multicenter trial with almost 12,000 randomized acute MI patients reported in *The Lancet*
- 1.5 million units of streptokinase plus conventional therapy vs. conventional therapy alone
- 47% less mortality with IV streptokinase given within one hour of onset of chest pain
- 23% less mortality with IV streptokinase given within three hours
- 17% less mortality with IV streptokinase given within six hours
- Incidence of major and minor complications considered acceptable

Improved cardiac function with few adverse effects[2]

- Randomized, placebo-controlled trial with 172 first-infarction patients, reported in *New England Journal of Medicine*, Oct 1, 1987
- 1.5 million units of streptokinase plus conventional therapy (including anticoagulants) vs. placebo infusion plus conventional therapy within four hours of onset of chest pain
- Coronary artery reperfusion shown by earlier peak of myocardial creatine kinase
- Significant increase in left ventricular ejection fraction and significant reduction in end-systolic volume confirmed by left ventricular angiography
- In this study, the most serious adverse effect was manageable hypotension

Benefits beyond thrombolysis

- Decreases red blood cell aggregation, and plasma and blood viscosity[3-5]
- Reduces blood pressure and total peripheral resistance with corresponding reduction in cardiac afterload for reduced myocardial oxygen demand[6-8]

Timing, dosage, and patient selection criteria

- Earliest treatment gives the best results
- Dosage: 1.5 million international units of streptokinase; duration of infusion up to 60 minutes
- Risk vs. benefits must be considered.

—Contraindications include active internal bleeding; recent (within two months) cerebral vascular accident, intracranial or intraspinal injury; intracranial neoplasm; and severe, uncontrolled hypertension

—*Risk of bleeding:* From pooled data of studies of 8,369 patients, the overall incidence of major bleeding was 1.2%. Nonetheless, physicians should be alert to untoward bleeding events. (Consult Warnings section of Streptase full prescribing information.)

Please see references and brief summary of prescribing information at end of this advertisement.

Intravenous

Streptase®

In the critical hours of acute MI

For acute MI
Intravenous

Streptase®
(Streptokinase)

The only thrombolytic that provides all these important benefits:

Proof of increased survival
- Reduction in mortality documented in a randomized study with almost 12,000 patients[1]

Proof of improved cardiac function
- Angiographic confirmation of improved left ventricular function[2]

Unique actions for greater reductions in cardiac stress
- Extrathrombolytic activity—reduces blood pressure, red blood cell aggregation, and blood and plasma viscosity[3-8]

Speed and simplicity in a one-step regimen
- Convenient, 1-hour constant-rate infusion compared to a 3 hour variable rate infusion with tissue plasminogen activator (r-TPA)

Staff confidence through many years of experience
- 10 years' experience in U.S. hospitals—and 25 years' worldwide—in lytic therapy

A tradition of service and support
- Extensive inservice training, important speakers' programs, and personal service by 650 skilled representatives to meet your hospital's needs

...all this at 90% less cost
- Priced at less than 10% of the reported cost of tissue plasminogen activator (r-TPA)

Bleeding, allergy and fever are the most frequent side effects seen with streptokinase; during treatment of myocardial infarction, hypotension and arrhythmias have been reported. Please see Warnings section of prescribing information before using Streptase®.

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Intravenous Streptase®
Clearly different...clearly the thrombolytic of choice.

Manufactured by:
Behringwerke AG, Marburg, West Germany.

Distributed by:
Hoechst-Roussel Pharmaceuticals Inc.
Somerville, New Jersey 08876

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Q70064-1087

References: 1. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardio (GISSI): Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;Feb 22:397-402. 2. White HD, Norris RM, Brown MA, et al: Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. *N Engl J Med* 1987;317(14): 850-855. 3. Ehrly A: Hemodilution. Theoretical basis and clinical application. *Int Symp Rottach-Egern* 1971;289-297. 4. Theiss W, Volger E, Wirtzfeld A, Keisel I, Blomer H: Coagulation studies after intravenous short-term streptokinase in acute myocardial infarction. *Klin Wochenschr* 1980;58:607-615. 5. Jan K-M, Reinhart W, Chien S, et al: Altered rheological properties of blood following administrations of tissue plasminogen activator and streptokinase in patients with acute myocardial infarction. *Circulation* 1985;72(Part II): III 417. 6. Neuhof H, Hey E, Glaser E, Wolf H, Lasch H: Hemodynamic reactions induced by streptokinase therapy in patients with acute myocardial infarction. *Eur J Intensive Care Med* 1975;1:27-30. 7. European Cooperative Study Group: *Acta Med Scand* 1981;Suppl 648:7-57. 8. Data on file. Hoechst-Roussel Pharmaceuticals Inc.

STREPTASE®
(Streptokinase)

Brief Summary
Consult full prescribing information before using.

INDICATIONS AND USAGE
Acute Evolving Transmural Myocardial Infarction
Streptase®, Streptokinase, is indicated for use in the management of acute myocardial infarction in adults, for the lysis of intracoronary thrombi, for the improvement of ventricular function, and reduction of mortality when administered by either the intravenous or intracoronary route. Earlier administration of Streptokinase is correlated with greater clinical benefit. See CLINICAL PHARMACOLOGY section of full prescribing information.

CONTRAINDICATIONS
Because thrombolytic therapy increases the risk of bleeding, Streptase®, Streptokinase, is contraindicated in the following situations:
- —Active internal bleeding
- —Recent (within 2 months) cerebrovascular accident, intracranial or intraspinal surgery (see WARNINGS)
- —Intracranial neoplasm
- —Severe uncontrolled hypertension.

Streptokinase should not be administered to patients having experienced severe allergic reaction to the product.

WARNINGS
Bleeding
Streptase®, Streptokinase, will cause lysis of hemostatic fibrin deposits such as those occurring at sites of needle punctures, and bleeding may occur from such sites. In order to minimize the risk of bleeding during treatment with Streptokinase, venipunctures and physical handling of the patient should be performed carefully and as infrequently as possible, and intramuscular injections must be avoided.
Should arterial puncture be necessary during intravenous therapy, upper extremity vessels are preferable. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.
In the following conditions the risks of therapy may be increased and should be weighed against the anticipated benefits.
- —Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels
- —Recent (within 10 days) serious gastrointestinal bleeding
- —Recent (within 10 days) trauma including cardiopulmonary resuscitation
- —Hypertension: systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg
- —High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- —Subacute bacterial endocarditis
- —Hemostatic defects including those secondary to severe hepatic or renal disease
- —Pregnancy
- —Cerebrovascular disease
- —Diabetic hemorrhagic retinopathy
- —Septic thrombophlebitis or occluded AV cannula at seriously infected site
- —Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Should serious spontaneous bleeding (not controllable by local pressure) occur, the infusion of Streptase®, Streptokinase, should be terminated immediately and treatment instituted as described under ADVERSE REACTIONS.

Arrhythmias
Rapid lysis of coronary thrombi has been shown to cause reperfusion atrial or ventricular dysrhythmias requiring immediate treatment. Careful monitoring for arrhythmia is recommended during and immediately following administration of Streptase®, Streptokinase, for acute myocardial infarction.

Hypotension
Hypotension, sometimes severe, not secondary to bleeding or anaphylaxis has been observed during intravenous Streptase®, Streptokinase, infusion in 1% to 10% of patients. Patients should be monitored closely and, should symptomatic or alarming hypotension occur, appropriate treatment should be administered. This treatment may include a decrease in the intravenous Streptokinase infusion rate. Smaller hypotensive effects are common and have not required treatment.

Other
Non-cardiogenic pulmonary edema has been reported rarely in patients treated with Streptase®, Streptokinase. The risk of this appears greatest in patients who have large myocardial infarctions and are undergoing thrombolytic therapy by the intracoronary route.
Rarely, polyneuropathy has been temporally related to the use of Streptase®, Streptokinase.
Should pulmonary embolism or recurrent pulmonary embolism occur during Streptase®, Streptokinase, therapy, the originally planned course of treatment should be completed in an attempt to lyse the embolus. While pulmonary embolism may occasionally occur during Streptokinase treatment, the incidence is no greater than when patients are treated with heparin alone.

PRECAUTIONS
General
Because of the increased likelihood of resistance, due to antistreptokinase antibody, Streptase®, Streptokinase, may not be effective if administered between five days and six months of prior Streptokinase administration or streptococcal infections, such as streptococcal pharyngitis, acute rheumatic fever, or acute glomerulonephritis secondary to a streptococcal infection.

Laboratory Tests
Intravenous or Intracoronary Infusion for Myocardial Infarction
Intravenous administration of Streptase®, Streptokinase, will cause marked decreases in plasminogen and fibrinogen and increases in thrombin time (TT), activated partial thromboplastin time (APTT), and prothrombin time (PT). These changes may also occur in some patients with intracoronary administration of Streptokinase.
Intravenous Infusion for Other Indications. Before commencing thrombolytic therapy, it is desirable to obtain an activated partial thromboplastin time (APTT), a prothrombin time (PT), a thrombin time (TT), fibrinogen levels, and a hematocrit and platelet count. If heparin has been given, it should be discontinued and the TT or APTT should be less than twice the normal control value before thrombolytic therapy is started.
During the infusion, decreases in plasminogen and fibrinogen levels and an increase in the level of FDP (the latter two causing a prolongation in the clotting times of coagulation tests) will generally confirm the existence of a lytic state. Therefore, lytic therapy can be confirmed by performing the TT, APTT, PT, or fibrinogen levels approximately 4 hours after initiation of therapy. If heparin is to be (re)instituted following the Streptase®, Streptokinase, infusion, the TT or APTT should be less than twice the normal control value (see manufacturer's prescribing information for proper use of heparin).

Drug Interactions
The interaction of Streptase®, Streptokinase, with other drugs has not been well studied.
Use of Anticoagulants and Antiplatelet Agents. Streptase®, Streptokinase, alone or in combination with antiplatelet agents and anticoagulants, may cause bleeding complications. Therefore, careful monitoring is advised. Concurrent use of antiplatelet agents such as aspirin, dipyridamole, or nonsteroidal antiinflammatory agents is not recommended.
Anticoagulation After Treatment for Myocardial Infarction. The administration of anticoagulant and/or antiplatelet drugs following administration of Streptase®, Streptokinase, appears to increase the risk of bleeding (see ADVERSE REACTIONS). These agents have been used in an attempt to prevent reocclusion of the target vessel. Use of anticoagulants or antiplatelet drugs following administration of Streptokinase has not yet been shown to be of unequivocal clinical benefit. Therefore, the use of anticoagulant and/or antiplatelet regimens should be individualized.
Anticoagulation after IV Treatment for Other Indications. Continuous intravenous infusion of heparin, without a loading dose, has been recommended following termination of Streptase®, Streptokinase, infusion for treatment of pulmonary embolism or deep vein thrombosis to prevent rethrombosis. The effect of Streptokinase on thrombin time (TT) and activated partial thromboplastin time (APTT) will usually diminish within 3 to 4 hours after Streptokinase therapy, and heparin therapy without a loading dose can be initiated when the TT or the APTT is less than twice the normal control value.

Pregnancy
Pregnancy Category C. Animal reproduction studies have not been conducted with Streptase®, Streptokinase. It is also not known whether Streptokinase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Streptokinase should be given to a pregnant woman only if clearly needed.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
The following adverse reactions have been associated with intravenous therapy and may also occur with intracoronary artery infusion:

Bleeding
The incidence of bleeding (major or minor) varied widely from study to study depending on dosage, patient population and concomitant therapy.
Minor bleeding can be anticipated mainly at invaded or disturbed sites. If such bleeding occurs, local measures should be taken to control the bleeding.
Severe internal bleeding involving gastrointestinal, genitourinary, retroperitoneal, or intracerebral sites has occurred and has resulted in fatalities. In three studies in which anticoagulation was optional following intravenous administration of Streptase®, Streptokinase, for acute myocardial infarction, the incidence of major bleeding ranged from 0.3%-6.2%. In 21 studies in which anticoagulation was compulsory, the incidence of major bleeding ranged from 0-16%. The overall incidence of major bleeding with intravenous infusion is 1%-2%.
Major bleed rates are difficult to determine for other dosages and patient populations because of the different dosing and intervals of infusions. The rates reported appear to be within the ranges reported for intravenous administration in acute myocardial infarction.
Should uncontrollable bleeding occur, Streptokinase infusion should be terminated immediately. Slowing the rate of administration of Streptokinase will not help correct bleeding and may make it worse. If necessary, bleeding can be reversed and blood loss effectively managed with appropriate replacement therapy. Although the use of aminocaproic acid (ACA, AMICAR®) in humans as an antidote for Streptokinase has not been documented, it may be considered in an emergency situation.

Allergic Reactions
Anaphylactic and anaphylactoid reactions have been observed rarely in patients treated intravenously with Streptase®, Streptokinase. These ranged in severity from minor breathing difficulty to bronchospasm, periorbital swelling or angioneurotic edema. Other milder allergic effects such as urticaria, itching, flushing, nausea, headache and musculoskeletal pain have also been observed, as have delayed hypersensitivity reactions such as vasculitis and interstitial nephritis. Anaphylactic shock was reported in one study with an incidence rate of 0.1%.
Mild or moderate allergic reactions may be managed with concomitant antihistamine and/or corticosteroid therapy. Severe allergic reactions require immediate discontinuation of Streptase®, Streptokinase, with adrenergic, antihistamine, and/or corticosteroid agents administered intravenously as required.

Fever
Although Streptase®, Streptokinase, is nonpyrogenic in standard animal tests, recent reports in the literature have noted an incidence of fever ranging from 0 to 21% in patients treated intravenously with Streptokinase. Symptomatic treatment is usually sufficient to alleviate discomfort. The use of acetaminophen rather than aspirin is preferable.

DOSAGE AND ADMINISTRATION
Acute Evolving Transmural Myocardial Infarction
Administer Streptokinase as soon as possible after onset of symptoms. The greatest benefit in mortality reduction was observed when Streptase®, Streptokinase, was administered within one hour, statistically significant benefits were observed up to six hours and some benefit was observed up to 12 hours without statistical significance (see CLINICAL PHARMACOLOGY in full prescribing information).

Route	Total Dose	Dosage/Duration
Intravenous infusion	1,500,000 IU	1,500,000 IU within 60 min.

HOW SUPPLIED
Streptase®, Streptokinase, is supplied as a lyophilized white powder in 50 mL infusion bottles (1,500,000 IU) or in 6.5 mL vials with a color-coded label corresponding to the amount of purified Streptokinase in each vial as follows:
green— 250,000 IU
blue — 750,000 IU
red — 1,500,000 IU vials and infusion bottles.
Store unopened vials at controlled room temperature (15°-30°C or 59°-86°F). Unused reconstituted drug should be discarded.

Manufactured by: Behringwerke AG
US License No. 97
Distributed by: Hoechst-Roussel Pharmaceuticals Inc.
Somerville, NJ 08876

Edition 11/87A

Intravenous
Streptase®
(Streptokinase)
Now...for acute MI

Manufactured by:
Behringwerke AG, Marburg, West Germany.

Distributed by:
Hoechst-Roussel Pharmaceuticals Inc.
Somerville, New Jersey 08876

Hoechst

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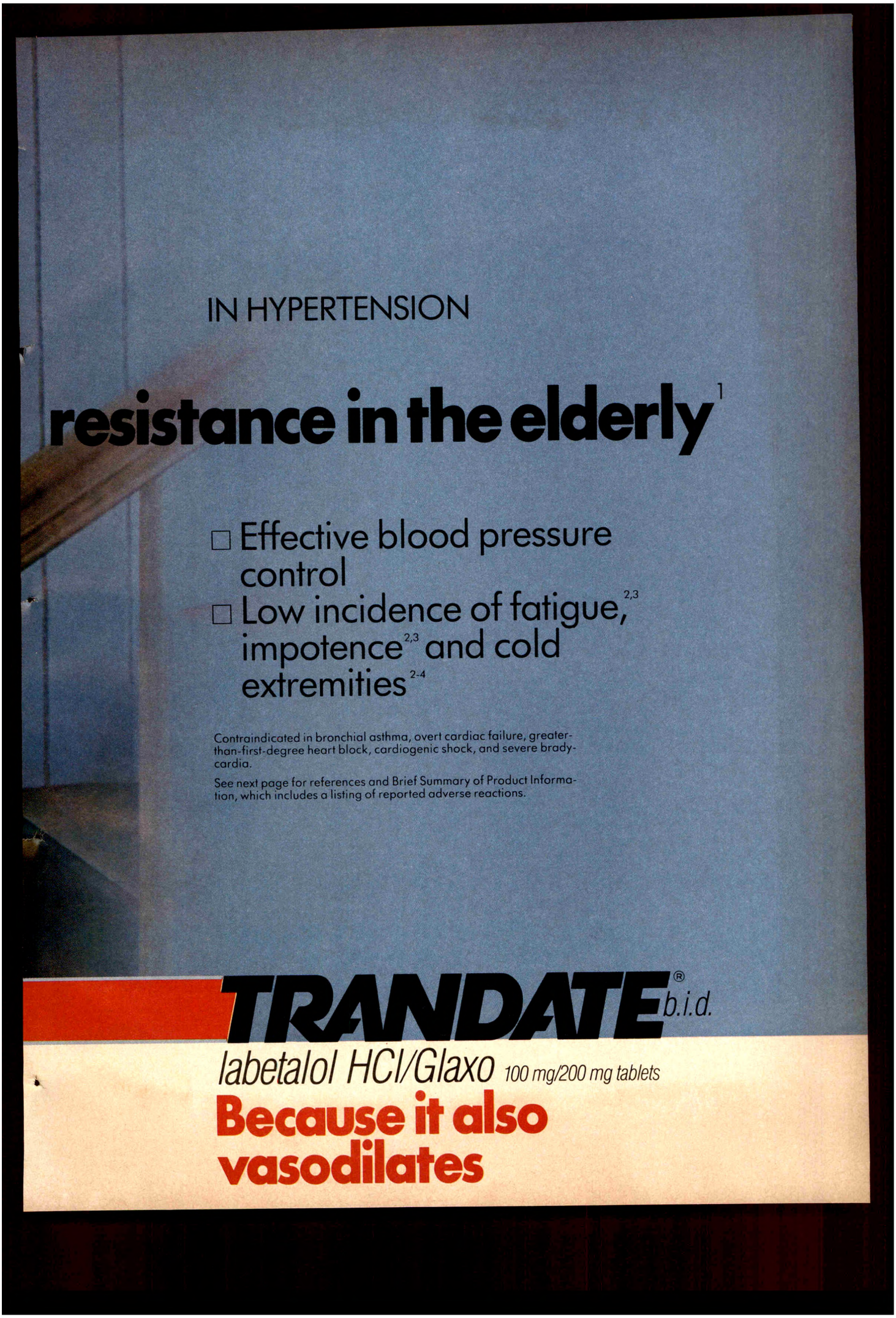
Glaxo


IN HYPERTENSION
resistance in the elderly[1]
☐ Effective blood pressure control
☐ Low incidence of fatigue,[2,3] impotence[2,3] and cold extremities[2-4]
Contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia.
See next page for references and Brief Summary of Product Information, which includes a listing of reported adverse reactions.
TRANDATE® b.i.d.
labetalol HCl/Glaxo 100 mg/200 mg tablets
Because it also vasodilates

References: 1. Holtzman JL, Finley D, Johnson B, et al: The effects of single-dose atenolol, labetalol, and propranolol on cardiac and vascular function. *Clin Pharmacol Ther* 1986;40:268-273. **2.** Due DL, Giguere GC, Plachetka JR: Postmarketing comparison of labetalol and propranolol in hypertensive patients. *Clin Ther* 1986;8(6):624-631. **3.** Burris JF, Goldstein J, Zager PG, et al: Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:1-9. **4.** Erb RJ, Plachetka JR: Thermographic evaluation of the peripheral vascular effects of labetalol and propranolol. *Curr Ther Res* 1985;28(1):68-73.

TRANDATE® Tablets
(labetalol hydrochloride)

BRIEF SUMMARY OF PRODUCT INFORMATION

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

INDICATIONS AND USAGE: TRANDATE® Tablets are indicated in the management of hypertension. TRANDATE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).

PRECAUTIONS: General: ***Impaired Hepatic Function:*** TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies have been performed with

labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multi-center, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, and headache.
Gastrointestinal: Nausea (6%), vomiting, dyspepsia, diarrhea, and taste distortion.
Central and Peripheral Nervous Systems: Dizziness (11%), paresthesia, and drowsiness.
Autonomic Nervous System: Nasal stuffiness, ejaculation failure, impotence, and increased sweating.
Cardiovascular: Edema and postural hypotension.
Respiratory: Dyspnea.
Skin: Rash.
Special Senses: Vision abnormality and vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including rarely, syncope.
Central and Peripheral Nervous Systems: Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment.
Collagen Disorders: Systemic lupus erythematosus; positive antinuclear factor (ANF).
Eyes: Dry eyes.
Immunological System: Antimitochondrial antibodies.
Liver and Biliary System: Cholestasis with or without jaundice.
Musculoskeletal System: Muscle cramps; toxic myopathy.
Respiratory System: Bronchospasm.
Skin and Appendages: Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia.
Urinary System: Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance or neuropsychometrics.
Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).
Allergic: Fever combined with aching and sore throat; laryngospasm; respiratory distress.
Hematologic: Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.
Gastrointestinal: Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

HOW SUPPLIED: TRANDATE® Tablets, 100 mg, light orange, round, scored, film-coated tablets engraved on one side with "TRANDATE 100 GLAXO," bottles of 100 (NDC 0173-0346-43) and 500 (NDC 0173-0346-44) and unit dose packs of 100 tablets (NDC 0173-0346-47).

TRANDATE Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with "TRANDATE 200 GLAXO," bottles of 100 (NDC 0173-0347-43) and 500 (NDC 0173-0347-44) and unit dose packs of 100 tablets (NDC 0173-0347-47).

TRANDATE Tablets, 300 mg, peach, round, scored, film-coated tablets engraved on one side with "TRANDATE 300 GLAXO," bottles of 100 (NDC 0173-0348-43) and 500 (NDC 0173-0348-44) and unit dose packs of 100 tablets (NDC 0173-0348-47).

TRANDATE Tablets should be stored between 2° and 30°C (36° and 86°F). TRANDATE Tablets in the unit dose boxes should be protected from excessive moisture.

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September 1986

Glaxo Inc.
Research Triangle Park, NC 27709

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617 Effect of Increasing Heart Rate on Left Ventricular Performance in Patients with Normal Cardiac Function

Saul Schaefer, Anne L. Taylor, Howard R. Lee, Elaine H. Niggemann, Benjamin D. Levine, Jeffrey J. Popma, Jere H. Mitchell, and L. David Hillis

In 19 patients with normal left ventricular (LV) function and coronary arteries, LV dP/dt max was measured at baseline heart rate and during incremental atrial pacing. In the 10 patients in whom intravascular volume was not altered during pacing, dP/dt max increased modestly (13 ± 16%); in contrast, in the 9 in whom normal saline was infused during pacing to maintain a constant LV preload, dP/dt max increased substantially (36 ± 17%) ($p = 0.007$). Thus, an increase in heart rate induces a modest increase in LV dP/dt max in patients in whom LV preload is allowed to decrease, whereas it causes a marked increase in dP/dt max in those in whom LV preload is maintained.

621 Intrinsic Left Ventricular Contractility in Normal Subjects

Marvin W. Kronenberg, Jack P. Uetrecht, William D. Dupont, Michael H. Davis, Brian K. Phelan, and Gottlieb C. Friesinger

The influence of autonomic tone and exercise stress on left ventricular (LV) contractility was assessed in 12 normal subjects using the relation of peak-systolic pressure to end-systolic volume (pressure-volume relation) and the ratio of peak-systolic pressure to end-systolic volume (pressure/volume ratio). Cuff blood pressure and gated equilibrium radionuclide ventriculography were employed at rest, during exercise and during pharmacologic pressure-afterloading with phenylephrine, both before and after vagal and β-adrenergic "blockade." Both the pressure/volume ratio and ejection fraction increased on exercise ($p \leq 0.008$). The pressure-volume relations were linear after blockade and there was no systematic difference in the slope of pressure-volume relations induced by blockade. Serial studies in 6 subjects showed no significant differences. Thus, vagal and β-adrenergic tone are not important for supporting LV contractility in normal subjects. The reproducibility of the measurements supports the feasibility of serial studies of contractility.

628 Strategies for Increasing Early Adherence to and Long-Term Maintenance of Home-Based Exercise Training in Healthy Middle-Aged Men and Women

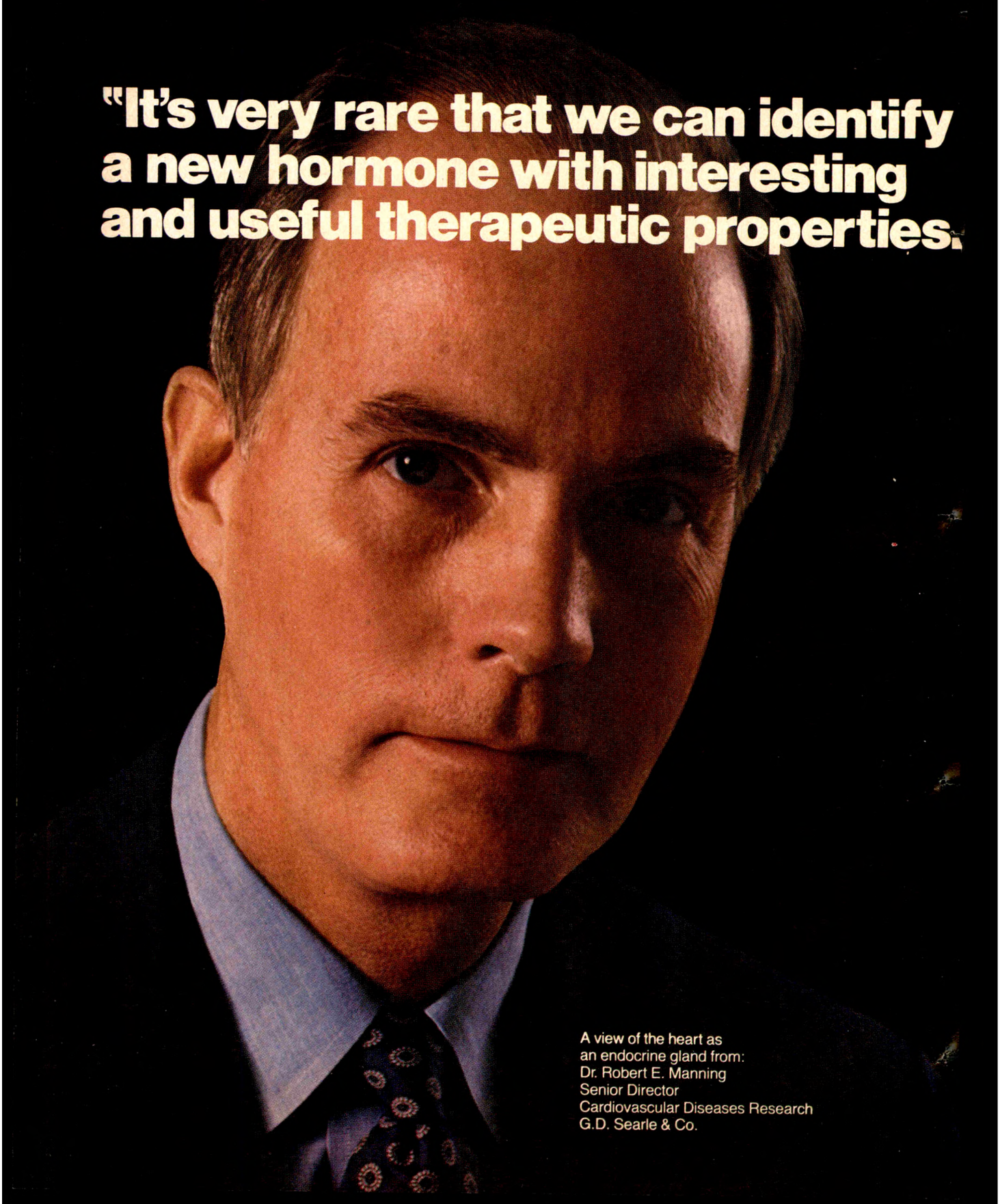
Abby C. King, C. Barr Taylor, William L. Haskell, and Robert F. DeBusk

Strategies for the adoption and maintenance of moderate-intensity, home-based exercise training were evaluated in 52 men and 51 women who had participated in a 6-month-long randomized trial of moderate-intensity, home-based exercise training. The adoption study compared 2 levels of intensity of staff support. Among subjects adopting exercise for the first time, functional capacity increased significantly only in those receiving more intensive staff support. The maintenance study compared

Continued on page A70

THE NEW VISION OF

"It's very rare that we can identify a new hormone with interesting and useful therapeutic properties.



A view of the heart as
an endocrine gland from:
Dr. Robert E. Manning
Senior Director
Cardiovascular Diseases Research
G.D. Searle & Co.

RESEARCH FROM SEARLE

Atrial peptides fill that bill."

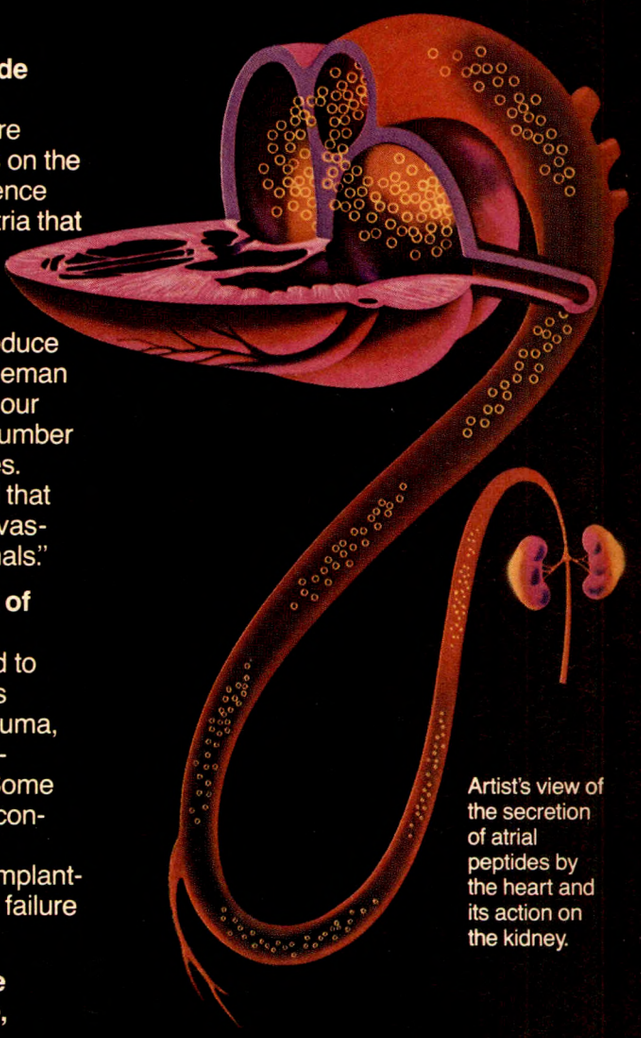
"We have been actively involved in atrial peptide research from the outset."
"The atrial peptides appear to be hormones that are released from the heart and have profound effects on the cardiovascular system. The first clue to their existence came from the discovery of small bodies in both atria that looked like secretory granules. The density of these granules was shown to vary with changes in sodium and water balance.

"Extracts of atrium were demonstrated to produce a marked diuresis in rats. This led Dr. Philip Needleman and his associates to enter into collaboration with our peptide chemists. We worked together—as did a number of other groups—to isolate a family of atrial peptides. The circulating form is a 28-amino acid compound that causes diuresis, natriuresis, relaxation of isolated vascular strips and lowering of blood pressure in animals."

"Atrial peptides may be useful in the treatment of acute renal failure."
"Certain of the atrial peptides have been observed to cause a selective renal vasodilation. This suggests their possible use in renal shutdown caused by trauma, abdominal surgery, suprarenal aortic clamping, immunosuppressant therapy and hepatic cirrhosis. Some of these disease states are characterized by vasoconstriction.

"Continuous administration by some sort of implantable pump might have major value in chronic renal failure and postpone the need for dialysis."

"Even more important, atrial peptides could be natural hormonal regulators of blood pressure, blood volume and electrolyte balance."
"Hopefully, this concept may lead us to related therapeutic agents that could be orally administered and would have a long duration of action. Such agents could have significant potential for the treatment of hypertension, congestive heart failure, and a number of fluid and electrolyte disorders."



Artist's view of the secretion of atrial peptides by the heart and its action on the kidney.

SEARLE

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2 levels of intensity of self-monitoring. Among subjects maintaining exercise, functional capacity remained equally high in subjects performing more and less intensive self-monitoring. Brief instruction followed by regular telephone contact with staff can be used to help people adopt a moderate-intensity, home-based exercise training program that can be maintained by simple self-monitoring strategies.

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ADD CAPOTEN® SOONER*...

(captopril tablets)

SQUIBB

COMPLETE THE JOB YOUR LOOP DIURETIC STARTED

In patients symptomatic on diuretic and digitalis

- ☐ Adding CAPOTEN enhances the diuretic effect of furosemide
  —Disappearance of edema in 55% of a subgroup of patients after adding CAPOTEN to furosemide†[1]
- ☐ Adding CAPOTEN improves exercise tolerance times in mild, moderate, and severe heart failure patients[2]

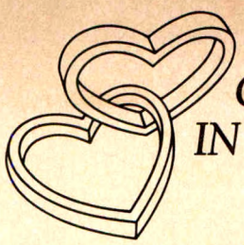
IN MILD, MODERATE, AND SEVERE HEART FAILURE (NYHA Class II, III, and IV)

CAPOTEN®
(captopril tablets)

CLOSING THE LOOP IN HEART FAILURE THERAPY

*CAPOTEN is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. See INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS in the brief summary of prescribing information on adjacent page.

†Patients for whom data were available for two months. Patients were NYHA Class II, III, or IV receiving concomitant diuretic and digitalis therapy.



CLOSING THE LOOP IN HEART FAILURE THERAPY

SQUIBB

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia ($< 1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $< 1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* – Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* – If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension – Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

References:

1. The Captopril Multicenter Research Group I: A cooperative multicenter study of captopril in congestive heart failure: Hemodynamic effects and long-term response. Am Heart J 110: 439-447, 1985.
2. Captopril Multicenter Research Group: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Coll Cardiol 2:755-763, 1983.

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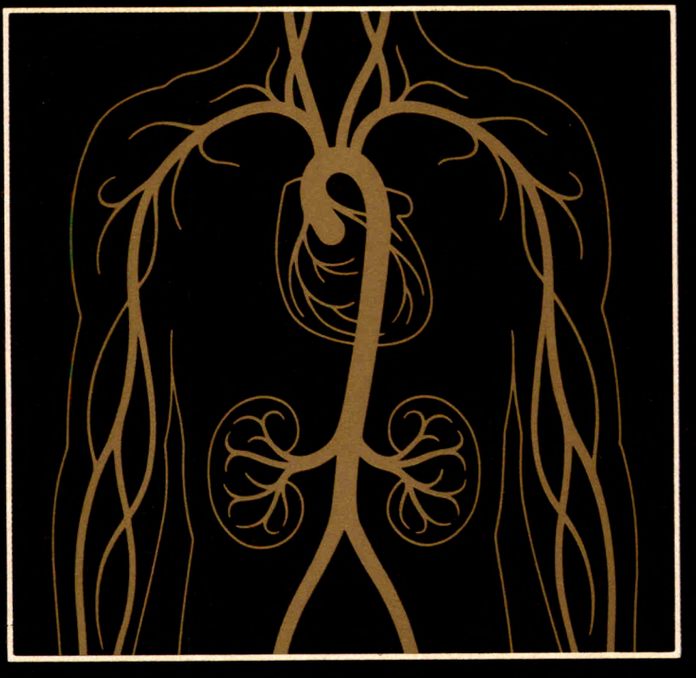

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BRIEF SUMMARY

Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure<90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present).

Warnings: Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction<30%) or moderate to severe symptoms of cardiac failure and in patients with significant ventricular dysfunction if they are receiving a beta-adrenergic blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce a decrease in blood pressure below normal levels, which may result in dizziness or symptomatic hypotension. Elevations of liver enzymes have been reported. Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). The effect of verapamil on AV conduction and the SA node may cause asymptomatic 1st-degree AV block and transient bradycardia, sometimes with nodal escape rhythms. PR-interval prolongation is correlated with verapamil plasma concentrations especially during initial titration. Higher degrees of AV block are infrequent (0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Studies in a small number of patients suggest that concomitant use of Calan and oral beta-adrenergic blockers may be beneficial in certain patients with chronic stable angina or hypertension. Combined therapy can also have adverse effects on cardiac function; therefore patients should be closely monitored. A decrease in metoprolol clearance may occur with concurrent use of verapamil and metoprolol. Chronic verapamil treatment increases serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient reassessed. Verapamil used concomitantly with oral antihypertensive agents will usually have an additive effect on lowering blood pressure that in some cases may be excessive; therefore patients should be monitored appropriately. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Quinidine levels may increase during verapamil therapy. Clearance of verapamil may be reduced in concomitant use with cimetidine. Concomitant use of verapamil and lithium may result in decreased serum lithium levels. Verapamil therapy may increase carbamazepine concentrations during combined use. Therapy with rifampin may markedly reduce oral verapamil bioavailability. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Another study in rats showed no evidence of carcinogenicity. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy in children under 18 have not been established.

Adverse Reactions— oral verapamil: Constipation (8.4%), dizziness (3.5%), nausea (2.7%), hypotension (2.5%), edema (2.1%), headache (1.9%), CHF/pulmonary edema (1.8%), fatigue (1.7%), bradycardia: HR <50/min (1.4%), AV block: total 1°, 2°, 3° (1.3%)/3rd-degree (0.8%), flushing (0.1%); elevations of liver enzymes have been reported (see *Warnings*). The following reactions, reported in 1.0% or less of patients, occurred under circumstances where a causal relationship is not certain: angina pectoris, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, dyspnea, arthralgia, rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, blurred vision, gynecomastia, impotence, increased urination, spotty menstruation.

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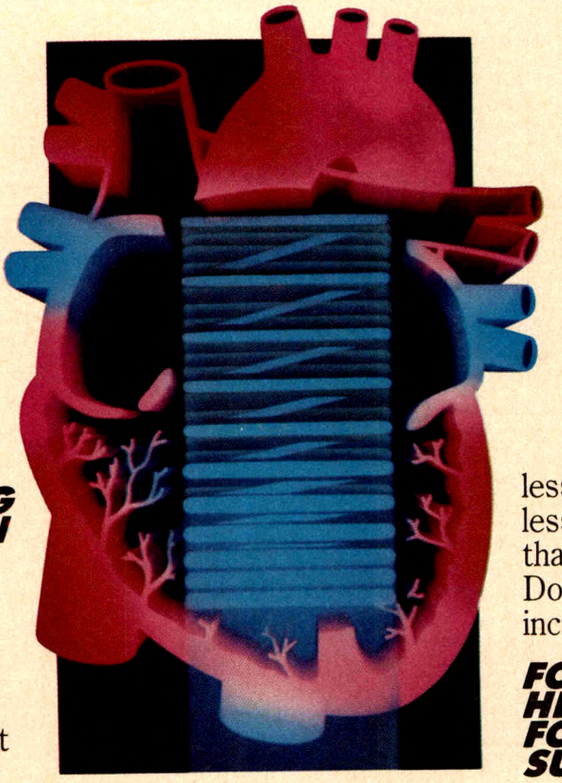

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Dobutrex® Solution

dobutamine hydrochloride injection

Brief Summary. Consult the package insert for prescribing information.

Clinical Pharmacology: Dobutrex Solution is a direct-acting inotropic agent whose primary activity results from stimulation of the ß receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. In animal studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.

In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.

Facilitation of atrioventricular conduction has been observed in human electrophysiologic studies and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

Most clinical experience with dobutamine is short-term—up to several hours in duration. In the limited number of patients who were studied for 24, 48, and 72 hours, a persistent increase in cardiac output occurred in some, whereas the output of others returned toward baseline values.

The onset of action of Dobutrex Solution is within one to two minutes; however, as much as ten minutes may be required to obtain the peak effect of a particular infusion rate.

The plasma half-life of dobutamine in humans is two minutes. The principal routes of metabolism are methylation of the catechol and conjugation. In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The 3-O-methyl derivative of dobutamine is inactive.

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine in animals, which indicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

Indications and Usage: Dobutrex Solution is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with Dobutrex.

Contraindications: Dobutrex Solution is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to Dobutrex.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex Solution may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10% of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5% have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex Solution may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

3. *Hypersensitivity*—Reactions suggestive of hypersensitivity associated with administration of Dobutrex Solution, including skin rash, fever, eosinophilia, and bronchospasm, have been reported occasionally.

4. Dobutrex Solution contains sodium bisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Precautions: 1. During the administration of Dobutrex Solution, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex Solution.

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex Solution is instituted.

3. Animal studies indicate that dobutamine may be ineffective if the patient has recently received a ß-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex Solution following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex Solution for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clincial studies in which Dobutrex Solution was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10- to 20-mm increase in systolic blood pressure and an increase in heart rate of 5 to 15 beats/minute have been noted in most patients. (*See* Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5% of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3% of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex Solution have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex Solution until the patient's condition stabilizes. Because the duration of action of Dobutrex Solution is short, usually no additional remedial measures are necessary.

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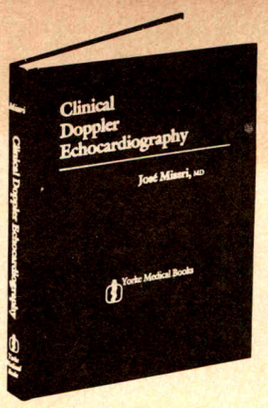

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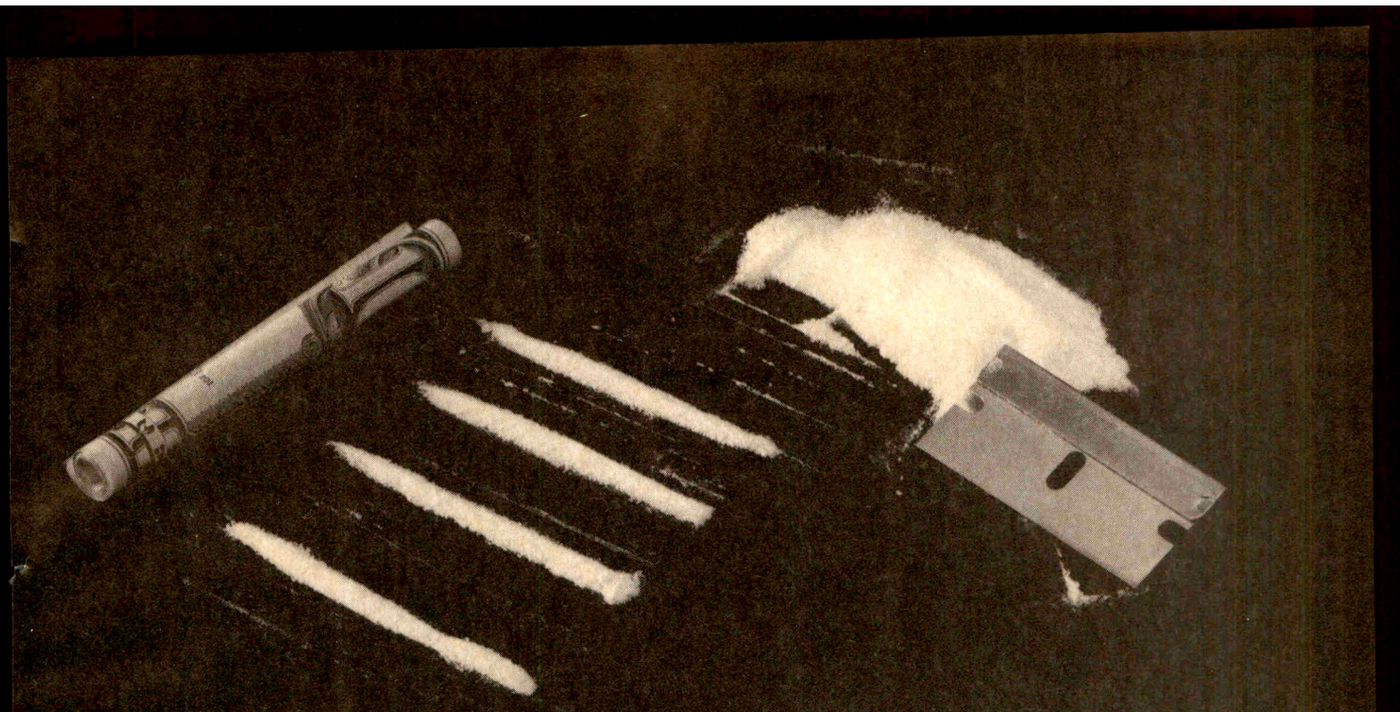

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Effects of Encainide, Flecainide, Imipramine and Moricizine on Ventricular Arrhythmias During the Year After Acute Myocardial Infarction: The CAPS

THE CARDIAC ARRHYTHMIA PILOT STUDY (CAPS) INVESTIGATORS*

The National Heart, Lung, and Blood Institute initiated the Cardiac Arrhythmia Pilot Study (CAPS) to evaluate the feasibility of suppressing ventricular arrhythmias after acute myocardial infarction. Ten centers enrolled 502 patients younger than 75 years of age with ≥10 ventricular premature complexes (VPC) per hour in a 24-hour electrocardiographic recording and a left ventricular ejection fraction >20%. Patients were enrolled 6 to 60 days after acute myocardial infarction and randomized to 1 of 5 treatment tracks with 2 drugs that included encainide, flecainide, imipramine, moricizine or placebo. During a double-blind drug and dose selection phase, investigators were permitted to change drug or dosage to achieve ≥70% suppression in VPC frequency and >90% suppression of runs of VPC with the exception of patients assigned to placebo, who continued receiving it. Patients were followed for a year after randomization. Patients in the 5 treatment arms were similar in age, sex, clinical characteristics, VPC frequency, left ventricular ejection fraction and concomitant drug treatment. As first drugs, encainide and flecainide had higher efficacy rates, 79% and 83%, respectively, than imipramine, 52%, moricizine, 66%, or placebo, 37%. Encainide and flecainide also had high efficacy rates, 68% and 69%, in patients who failed imipramine or moricizine. Encainide, flecainide and moricizine were well tolerated. These 3 drugs had intolerable adverse effect rates of 6% or less, i.e., similar to placebo. More than 70% of the patients who started the follow-up phase on encainide, flecainide or moricizine remained on these drugs to the end of the study. Imipramine had a high intolerable adverse effect rate. The results of CAPS indicate that large-scale clinical trials to evaluate the effect of ventricular arrhythmia suppression with antiarrhythmic drugs on mortality are feasible.

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Address for reprints: The CAPS Coordinating Center, University of Washington, JD-22, 1107 Northeast 45th, Room 505, Seattle, Washington 98105.

*Members of the Cardiac Arrhythmia Pilot Study (CAPS) are listed in the Appendix.

There is considerable evidence that the presence of ventricular premature complexes (VPCs) predict mortality after acute myocardial infarction (AMI).[1-6] Ruberman[1] showed that complex VPC in a 1-hour electrocardiographic recording identified patients at high risk for both total and sudden cardiac death. Moss et al[2] found that both frequency and complexity of VPC predicted sudden cardiac death and nonsudden cardiac death. Bigger et al[3] showed that ventricular arrhythmias predict mortality independent of left ventricular dysfunction assessed by New York Heart Association class, rales in the coronary care unit and left ventricu-

lar ejection fraction. Similarly, Mukharji et al[4] found that patients with ≥10 VPC/hour had a mortality rate nearly 4 times that of patients with <10 VPC/hour after adjusting for left ventricular ejection fraction.

Given the evidence available, it is reasonable to hope that suppression of ventricular arrhythmias after AMI with antiarrhythmic drugs will improve survival, but there is no significant evidence to support this hypothesis. Furberg[7] summarized the clinical trials in post-AMI patients and emphasized that methodologic problems could account for failure to observe a reduction in mortality with antiarrhythmic therapy. Problems included: (1) inadequate sample size; (2) failure to enroll patients with arrhythmias; (3) failure to assess antiarrhythmic effect; (4) lack of dose titration; and (5) no option to use a second drug if the first failed. Such methodologic problems may have compromised trials with phenytoin, aprindine, mexiletine and tocainide.[8–14]

The National Heart, Lung, and Blood Institute initiated the Cardiac Arrhythmia Pilot Study (CAPS) to obtain knowledge needed for planning a full-scale study to test the hypothesis that long-term suppression of ventricular arrhythmias after AMI with antiarrhythmic drugs will improve survival. Some of the objectives were to: (1) develop methods for identifying and recruiting patients post infarction arrhythmias; (2) develop methods for drug and dose determination in a double-blind clinical trial; (3) determine whether a treatment can suppress VPC rates by at least 70% in about 80% of patients; (4) assess the efficacy and adverse effects of antiarrhythmic drugs over a 1-year period; (5) characterize the natural history of ventricular arrhythmias in the year following AMI; and (6) evaluate the relation between behavioral factors and ventricular arrhythmias after AMI. The present report will provide the results related to the first 4 objectives.

Methods

CAPS was a double-blind, placebo-controlled, randomized trial conducted in 10 clinical centers, a coordinating center, a drug distribution center, a central ambulatory electrocardiogram reading center and the National Heart, Lung, and Blood Institute project office.[15,16] CAPS was divided into 3 phases: (1) patient recruitment; (2) drug and dose selection; and (3) follow-up.

TABLE I Doses of Drugs Used in the Cardiac Arrhythmia Pilot Study

Drug	Total Daily Dose (mg)		
	Low	Medium	High
Encainide	105	150	180
Flecainide	200	300	400
Imipramine	150	225	375
Moricizine	600	750	900

These drugs and a corresponding placebo were donated as follows: encainide by Bristol-Myers Research Laboratories; flecainide by Riker Laboratories; imipramine by Ciba-Geigy; moricizine by DuPont Pharmaceuticals.

Patient recruitment phase: Patients were eligible if they had AMI between 6 and 60 days before enrollment, were <75 years of age and demonstrated either an average of ≥10 VPC/hour or ≥5 episodes of unsustained ventricular tachycardia (3 to 9 consecutive VPCs with a rate of ≥100/min) in a qualifying 24-hour ambulatory electrocardiogram. Patients were excluded if they had a left ventricular ejection fraction ≤20%, contraindications to any of the study medications or ≥10 consecutive VPCs at a rate ≥100/min (disqualifying ventricular tachycardia). Patients with ≥10 consecutive VPCs were excluded because of the concern that their physicians often would want to treat them with conventional antiarrhythmic drugs. If there was inadequate VPC frequency in the first 24-hour ambulatory electrocardiogram, the patient could be screened once more up to 60 days after the AMI.

Drug/dose selection phase: The design of CAPS permitted a comparison of encainide, flecainide, imipramine and moricizine treatment with placebo (Figure 1). After qualifying and giving informed written consent, patients were randomly assigned to 1 of 4 active drugs or to a matching placebo. Three doses of the first drug were permitted (Table I). Dosing continued until efficacy, defined as ≥70% reduction of VPC and >90% reduction in unsustained ventricular tachycardia, was achieved. If efficacy was not achieved or if proarrhythmic effects, disqualifying ventricular tachycardia, conduction abnormalities or other intolerable adverse effects occurred, the patient was switched to a second drug in the treatment arm. Patients who started on a drug with class IC action (i.e., encainide or flecainide) were crossed over to a drug with class IA action (i.e., imipramine or moricizine) and vice versa (Figure 1). Up to 3 doses of the second drug also were permitted. If neither drug in a treatment arm was successful, patients were assigned to the drug that was more efficacious or better tolerated, or both. To detect and manage adverse effects, patients were hospitalized in a monitored setting during the first 48 hours of treatment with the first or second CAPS drug.

Definitions of adverse effects: The CAPS definition of proarrhythmic effect was published previously.[15] It required a 3- to 10-fold increase in VPC frequency and a return to baseline after drug discontinuation. Disqualifying ventricular tachycardia was defined as ≥10 consecutive VPCs at a rate ≥100/min. New or worsening heart failure was defined as hospitalization for heart failure or an increase in diuretic or digitalis dose occurring together with ≥2 signs or symptoms of heart failure, or both. Abnormalities in cardiac impulse formation or conduction were defined as heart rate of ≤30 lasting ≥1 minute, any pause in rhythm ≥3.5 seconds, second-degree Mobitz II atrioventricular block, third-degree atrioventricular block, QRS width ≥0.16 second or a QTc prolongation of ≥50% of the pretreatment control.

Placebo: The placebo comparison group was used to control for variability in VPC frequency during follow-up. Also, the placebo group provided a control for the evaluation of apparent adverse effects of active drugs. The use of placebo was considered ethical be-

cause there is no evidence that suppressing VPC after AMI will reduce the mortality rate. Patients who demonstrated lack of efficacy during treatment with placebo as their first drug were switched to a second placebo (Figure 1).

Follow-up phase: After a drug and dose were selected, patients were followed for 1 year after randomization. Change of study drug or adjustment of dosage was not allowed during the follow-up phase. Patients were evaluated by physical examination and ambulatory 24-hour electrocardiogram at 3, 6, 9 and 12 months. During follow-up, temporary suspension of study medication was allowed for certain surgical procedures and for recurrent myocardial infarction. In the absence of contraindications, the CAPS drug was then restarted. CAPS therapy was discontinued during the follow-up phase because of: (1) disqualifying ventricular tachycardia (≥10 consecutive VPCs); (2) conduction abnormalities; (3) proarrhythmic effect[15]; (4) other intolerable adverse effects; or (5) patient or primary physician decision. Although CAPS was not designed with enough power to assess the potential effect of drug treatment on major clinical events, total and cause-specific mortality and recurrent MI were monitored. After the 12-month evaluation, including a 24-hour continuous electrocardiographic recording, study medication was discontinued. At least 4 days after drug discontinuation, a second 12-month 24-hour electrocardiogram was recorded.

Statistical analysis: The design of CAPS was complex and many comparisons are possible. Because of the selective crossover design, the most valid comparison was by randomization group. However, this comparison obscures differences between drugs. Therefore, the main comparison of efficacy and the assessment of adverse effects of CAPS drugs were made by treatment arm at the end of dose titration on the first drug. Adverse effects during follow-up are presented for actual drug exposure rather than intention to treat because (although the potential for bias exists) it was thought that this was the more conservative and clinically meaningful approach. Comparisons of baseline variables between treatment arms were made by chi-square or analysis of variance, as appropriate. Proportions achieving efficacy or having adverse effects at the end of the drug and dose selection phase were compared by chi-square. Suppression of ventricular arrhythmias during the follow-up phase was evaluated by considering the proportion of patients with an average reduction of VPCs of at least 70% throughout the follow-up year. Percent suppression was computed by dividing the mean hourly VPC rates at the end of dosing, and at 3-, 6-, 9- and 12-month follow-up measures by the mean hourly rates of the baseline and all washout measures (usually the baseline and the 12-month washout). The time to a specific adverse event was analyzed by the method of Kaplan and Meier[17]; comparisons between failure time distributions were made using the log rank statistic.[18]

Results

Clinical characteristics: There were 502 patients enrolled in CAPS. At baseline, there were no overall statistically significant differences among the patients assigned to the 5 treatment arms with respect to age,

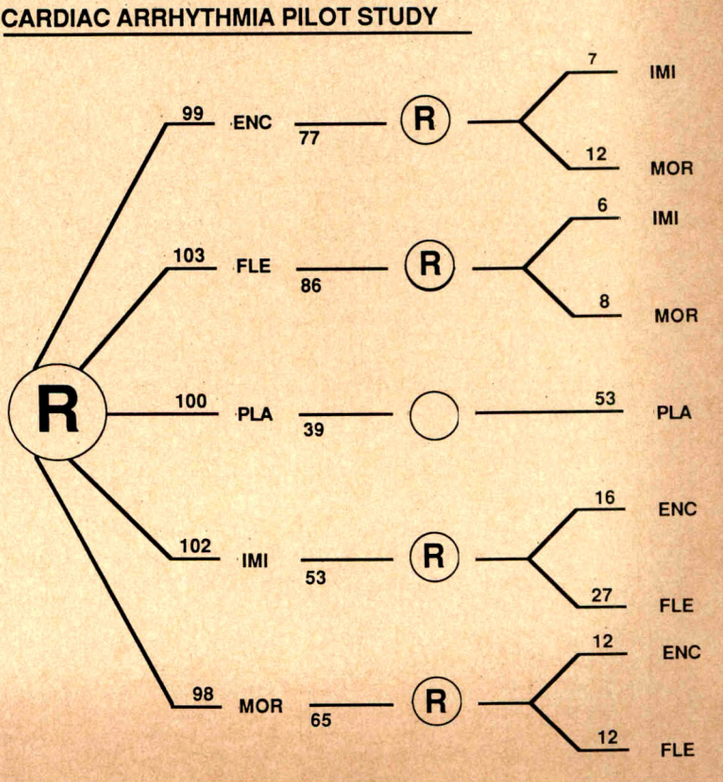

FIGURE 1. Design of the Cardiac Arrhythmia Pilot Study. The *left* column of numbers indicates the number of patients who were randomized to each treatment arm. The *middle* column indicates the number of patients who continued receiving the first drug. The *right* column indicates the number of patients who crossed to a second drug. ENC = encainide; FLE = flecainide; IMI = imipramine; MOR = moricizine; PLA = placebo; R = randomization. For additional information, see Table III.

TABLE II Comparison of Baseline Characteristics by Treatment Arm

Variable	First Drug in Treatment Arm					
	Encainide (n = 99)	Flecainide (n = 103)	Imipramine (n = 102)	Moricizine (n = 98)	Placebo (n = 100)	Total (n = 502)
Age (mean yrs)	59	59	59	59	60	59
Men (%)	85	82	84	85	81	83
Heart failure before AMI (%)	7	4	8	6	6	6
Previous AMI (%)	27	35	26	31	31	30
Family history of angina or AMI (%)	33	35	44	45	28	37
Diabetes mellitus (%)	17	24	9*	13	17	16
Cigarette smoker (%)	35	23	33	35	30	31
VPC/hour (mean)†	138	154	156	144	165	152
<30 (%)	46	36	29	32	30	34
30 to 99 (%)	23	33	32	30	30	30
≥100 (%)	30	31	39	38	40	36
LVEF (mean %)	45	45	46	44	45	45
≥40 (%)	65	63	66	65	67	65
Runs of 3–9 VPC (%)†	38	35	38	28	32	34
Drugs at baseline						
Digitalis (%)	18	25	26	26	20	23
Diuretics (%)	33	35	27	36	30	32
β-blockers (%)	46	36	43	37	41	41
Calcium antagonists (%)	34	51*	42	38	34	40
Potassium supplements (%)	16	16	14	12	18	15

* Statistically significant difference ($p < 0.05$); † dosing baseline Holter.

AMI = acute myocardial infarction; LVEF = left ventricular ejection fraction; VPC = ventricular premature complexes.

TABLE III Results During Drug and Dose Selection Phase of CAPS (n = 502)

	Treatment					
	Encainide	Flecainide	Imipramine	Moricizine	Placebo	Total
Randomized	99	103	102	98	100	502
Withdrew before treatment	1	0	0	0	1	2
Started on drug 1	98	103	102	98	99	500
During CAPS drug 1 dosing						
Withdrew	1	2	6	7	5	21
Died	1	1	0	2	2	6
Started CAPS drug 2 dosing	19	14	43	24	53	153
Continued CAPS drug 1	77	86	53	65	39	320
During CAPS drug 2 dosing						
From encainide	—	—	7	12	—	19
From flecainide	—	—	6	8	—	14
From imipramine	16	27	—	—	—	43
From moricizine	12	12	—	—	—	24
Withdrew	4	6	4	5	5	24
Died	0	0	0	1	0	1
Returned to CAPS drug 1	1	0	6	2	7	16
Continued CAPS drug 2	23	33	3	12	41	112
Returned to drug 1 from drug 2	8	0	1	0	7	16
By completion of drug and dose selection						
Assigned to CAPS drug	108	119	57	77	87	448
Withdrew	6	8	10	12	11	47
Died	1	1	0	3	2	7

sex, congestive heart failure, family history of coronary artery disease, smoking, average VPC/hour or ejection fraction (Table II).

Arrhythmia characteristics: All patients had ≥10 VPC/hour in their qualifying Holter recording. In the baseline tape for dosing, an average of 66% of patients (range 53 to 71%) assigned to each treatment arm had ≥30 VPC/hour (Table II); 36% (range 30 to 40%) had 100 VPC/hour or more; and 34% (range 28 to 38%) had 1 or more runs of unsustained ventricular tachycardia (3 to 9 consecutive VPCs).

Results during the drug and dose selection phase: Table III shows the results during the drug and dose selection phase. Two of the 502 patients enrolled withdrew before beginning treatment. During the first step of the drug and dose selection phase, 64% (320 pa-

tients) stayed on the first drug, 4.2% (21 of 500) patients withdrew and 1.2% died (6 of 500). There were 153 patients (31%) in whom CAPS drug 1 lacked efficacy or had intolerable adverse effects. These patients were randomized to CAPS drug 2, with 82% (23 of 28) of them remained on encainide and 85% (33 of 39) flecainide as a second drug, compared to imipramine (23%, 3 of 13) or moricizine (60%, 12 of 20). During dose titration with CAPS drug 2, a total of 112 patients continued receiving drug 2, 16 returned to their first drug, 24 patients withdrew and 1 died. By the completion of the drug and dose selection phase, 89% of the patients (448 of 502) were assigned to a CAPS drug for follow-up: encainide (108), flecainide (119), imipramine (57), moricizine (77) or placebo (87). Patient withdrawal was infrequent during the drug and dose selection phase; only 10.8% of patients either withdrew (9.4%) or died (1.4%).

Time between dose changes: The mean time between dose changes was 11 days during the drug and dose selection phase and was similar for each treatment. The number of days required to complete dosing was shorter for active treatment (encainide 16, flecainide 13, imipramine 20, moricizine 17) than for placebo (32). Patients randomized to placebo required an average of 3.0 dose titration steps compared to 1.7 for active treatment.

Results with CAPS drug 1: Three doses of CAPS drug were permitted and dose titration was continued until efficacy was reached or an adverse effect required switching to another drug in the treatment arm. Table IV describes efficacy and adverse effects of CAPS drug 1 at the completion of dose titration and the reasons for withdrawal during follow-up. Encainide (79%) and flecainide (83%) had higher efficacy rates (>70% VPC and >90% run reduction) than imipramine (52%), moricizine (66%) or placebo (37%) ($p < 0.01$). In addition, encainide, flecainide and moricizine were each more efficacious than placebo ($p < 0.001$). Except for imipramine, efficacy was observed in more patients (76%) with ejection fraction ≥45% than in patients with ejection fraction <45% (64%) ($p < 0.05$). For patients with low left ventricular ejection fraction (<30% or 30 to 44%) moricizine had efficacy rates similar to the drugs with class IC action. At the completion of dose titration on drug 1, there was no significant difference between any of the 5 treatments in the frequency of serious adverse cardiac effects confirmed by drug washout, such as proarrhythmic effect, disqualifying ventricular tachycardia (≥10 consecutive VPCs at a rate of >100/min), conduction abnormalities or heart failure. Imipramine had a 26% incidence of intolerable adverse effects documented by drug washout.

The number of patients who continued receiving the first drug differed: encainide, 85; flecainide, 86; imipramine, 54; moricizine, 65; and placebo, 46. Comparisons of reasons for withdrawal from these groups during follow-up must be viewed cautiously because they no longer contain all of the originally randomized patients. Disqualifying ventricular tachycardia, proarrhythmic effect or syncope that occurred during the follow-up phase, prompted withdrawal from CAPS drug 1 and disappeared during drug washout was seen in 7% of the patients on encainide, 7% on flecainide, 2% on imipramine, 6% on moricizine and 9% on placebo. Death or cardiac arrest occurred during the follow-up phase in 2% of the patients on encainide, 6% on flecainide, 7% on imipramine, 2% on moricizine and 4% on placebo as a first drug. At the end of the study, significantly more patients were taking encainide (64 of 99, 65%) and flecainide (64 of 103, 62%) as first drugs than placebo (35 of 100, 35%).

Results with CAPS drug 2: Findings at the completion of dose titration with CAPS drug 2 were similar to those with CAPS drug 1: encainide (68%) and flecainide (69%) were more effective than imipramine (15%) or moricizine (45%). There were no differences among the CAPS drugs, used as a second drug, in frequency of proarrhythmic effect, disqualifying ventricular tachycardia, conduction abnormalities or heart failure. At the end of the study, the percentage of patients who continued taking CAPS drug 2 were: encainide (20 of 23, 87%); flecainide (25 of 33, 76%); imipramine (2 of 3, 67%) and moricizine (9 of 12, 75%).

Adverse reactions and events in the first 48 hours: Because of concern that serious adverse effects might occur shortly after starting a CAPS drug, patients were hospitalized for at least 48 hours after beginning treatment. There were no differences among treatments with respect to frequency of adverse reactions or events in the first 48 hours (Table V). Serious adverse effects were rare and there were no early deaths that could be ascribed to CAPS treatment. Orthostatic hypotension occurred in 5 patients taking imipramine and was the most frequent early adverse effect.

Adverse effects during the follow-up phase: Reports of moderate to severe adverse effects were analyzed by drug treatment during the follow-up phase

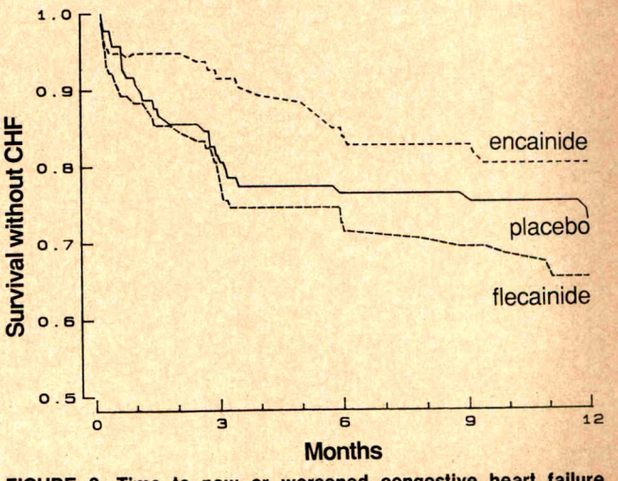

FIGURE 2. Time to new or worsened congestive heart failure (Kaplan-Meier method). Patients randomized to the placebo group, the encainide-imipramine/moricizine treatment arm, or the flecainide-imipramine/moricizine treatment arm are compared. Patients were censored when death or cardiac arrest occurred.

TABLE IV Results of Treatment with First Drug in the CAPS Treatment Arms

	Drug				
	Encainide (n = 99)	Flecainide (n = 103)	Imipramine (n = 102)	Moricizine (n = 98)	Placebo (n = 100)
During the Drug and Dose Selection Phase					
Effective (%)	79	83	52	66	37
LVEF <30%	67	64	47	55	22
LVEF 30–44%	69	79	59	64	36
LVEF ≥45%	90	91	49	73	41
Not effective* (%)	10	3	16	15	41
Adverse effects confirmed by drug washout					
Proarrhythmic (%)	1	3	1	1	3
Disqualifying VT (%)	1	2	2	2	6
Conduction abnormalities (%)	3	3	3	3	0
Heart failure (%)	0	2	1	0	0
Other intolerable adverse effects (%)	5	5	26	6	3
Not confirmed by drug washout					
Heart failure (%)	0	1	0	0	1
Death, cardiac arrest or VT (%)	1	1	0	4	2
Did not complete dosing and no probable cause ascribable (%)	2	0	2	4	7
During the Follow-Up Phase					
No. on drug 1 at end of dosing	85	86	54	65	46
No. on drug 1 at end of study	64	64	34	48	35
Reasons for withdrawal from drug 1					
Death or cardiac arrest (%)	2	6	7	2	4
VT, proarrhythmia or syncope (%)	7	7	2	6	9
Heart failure (%)	1	3	2	2	0
Recurrent infarction (%)	1	0	0	2	0
Other adverse effects (%)	7	6	17	9	4
Miscellaneous (%)	6	3	9	6	7

* Not effective without any serious adverse effect.

LVEF = left ventricular ejection fraction; VT = ventricular tachycardia (10 or more consecutive ventricular premature depolarizations).

TABLE V First CAPS Drug: Number of Adverse Reactions and Events in the First 48 Hours

	Drug					
Adverse Reaction or Event	Encainide (n = 99)	Flecainide (n = 103)	Imipramine (n = 102)	Moricizine (n = 98)	Placebo (n = 100)	Total (n = 502)
Death	0	0	0	0	0	0
Disqualifying ventricular tachycardia	1	0	2	1	1	5
Conduction abnormalities	0	0	0	1	2	3
Congestive heart failure	1	0	0	1	0	2
Recurrent myocardial infarction	0	0	0	1	2	3
Orthostatic hypotension	0	1	5	0	0	6
Other serious adverse effects	0	1	1	0	0	2
Total	2	2	8	4	5	21

(Table VI). The incidence of any adverse effect was lower for encainide (49%) and flecainide (55%) than for imipramine (67%), moricizine (64%) or placebo (60%). The most common *cardiovascular adverse effect* was dizziness upon standing for moricizine and imipramine (approximately 10%); *gastrointestinal adverse effects* (dry mouth, constipation) were seen most often after imipramine (44%); *genitourinary adverse effects* (decrease in sexual activity, difficulty urinating) occurred most often after encainide, flecainide and moricizine (15 to 18%); *neurologic adverse effects* (poor coordination, clumsiness or stumbling, dizziness or lightheadedness, numbness or tingling) were common for all treatments, including placebo (38%). Imipramine was the only treatment discontinued more frequently (18%) than placebo (7%) because of adverse symptoms (Table VI).

Heart failure: The actuarial 1-year incidence of heart failure was high in CAPS (25%). There was no statistically significant difference between all active treatments and placebo in the incidence of heart failure. In addition, there were no differences between the groups receiving encainide (20%) or flecainide (35%) and the placebo group (27%) (Figure 2).

Compliance: Compliance during the drug and dose selection phase was excellent for each treatment: 90%

TABLE VI Moderate to Severe Adverse Effects Reported Between the End of Drug and Dose Selection Phase and End of Follow-Up Phase (%)*

Category	Drug Assigned at End of Dosing				
	Encainide (n = 108)	Flecainide (n = 119)	Imipramine (n = 57)	Moricizine (n = 77)	Placebo (n = 87)
Cardiovascular	17	19	25	23	21
Dizziness on standing	5	5	9	10	0
Fast/irregular heart beat	6	5	2	10	8
Syncope or near syncope	2	3	5	1	2
Wheezing	6	6	2	8	5
Cutaneous†	3	3	4	6	3
Gastrointestinal‡	13	19	44	26	21
Genitourinary§	16	15	11	18	11
Neurologic‖	22	29	30	34	38
Other¶	31	32	37	44	43
Any symptom	49	55	67	64	60
Stopped drug because of symptom	2	3	18	6	7

* Only adverse effects reported while taking the drug assigned at the end of the drug and dose selection phase were counted; † burning or prickling of the skin; skin rash; ‡ dry mouth; nausea; vomiting; abdominal pain; diarrhea; constipation; § difficulty urinating; decrease in sexual activity; ‖ poor coordination; dizziness or lightheadedness; numbness or tingling; blurred vision; drowsiness; stuttering; tremor; nightmares; insomnia; ¶ headache; abnormal sense of well being; seeing or hearing things that aren't real; restlessness or nervousness; frequent depression that interferes with work, recreation or sleep; unusual tiredness or fatigue; fever.

had at least 80% compliance at each pill count (range 86 to 96%). During the follow-up phase, at least 80% compliance was noted in 71% taking encainide and 80% taking flecainide.

Mortality: There were no significant differences in mortality rate among the treatments. It was recognized during the design of CAPS that the number of fatal or major arrhythmic events would be insufficient to detect a treatment effect.

Discussion

Ventricular arrhythmias have been identified as an independent risk factor for cardiac mortality following AMI. To test the hypothesis that VPC suppression after AMI improves survival, adequate numbers of patients with significant ventricular arrhythmias will have to be enrolled, randomized to effective and tolerated antiarrhythmic agents or placebo and followed. To date, no large-scale clinical trials to test this hypothesis have been performed.[7] CAPS was undertaken to determine whether it is feasible to carry out such a study. The goals of CAPS were achieved, paving the way for a subsequent large-scale trial to assess effects of VPC suppression on mortality.

Feasibility: The CAPS showed that: (1) it is possible to identify and recruit suitable subjects for a definitive trial; (2) well tolerated, highly efficacious antiarrhythmic agents exist for ventricular arrhythmias after AMI; (3) dose titration with multiple drugs is feasible under clinical trial conditions; and (4) patient compliance and follow-up can be maintained in a postinfarction cohort. CAPS also showed that large numbers of patients must be screened to identify and enroll a sufficient number of qualified postinfarction patients.[16] Nearly 4,000 patients met other eligibility criteria and were screened with a 24-hour electrocardiographic recording to enroll 502 eligible patients. Additionally, CAPS showed that 2 drugs, encainide and flecainide, successfully suppress VPC after AMI, with no more adverse effects than placebo and with excellent compliance. Efficacy rates would have been lower and withdrawal rates higher had CAPS used only 1 dose level of 1 drug.

Drug efficacy and overall adverse effects with placebo: The placebo treatment arm permitted us to observe the natural history of ventricular arrhythmias after AMI. The apparent efficacy of 37% during dose titration with placebo reflected the high degree of spontaneous variability in VPC frequency and more frequent recording in the placebo group. The high frequency of apparent efficacy in this group must be considered in the design and analysis of any large-scale mortality reduction trial. The adverse effects encountered in the placebo treatment arm were compared with the active treatment arms. During treatment with a first drug (Table IV), there was no significant difference between placebo and active drugs in the incidence of conduction abnormalities, congestive heart failure or proarrhythmic effects. Similarly, in both the drug and dose selection and follow-up phases (Tables IV and VI), there was no difference between placebo, encainide, flecainide and moricizine in the incidence of intolerable noncardiac adverse effects.

Drug efficacy and overall adverse effects with active drugs: CAPS drugs with class IC action were more effective in suppressing ventricular arrhythmias than drugs with IA action. In both the drug and dose selection and follow-up phases, the efficacy of encainide and of flecainide was similar and superior to imipramine and moricizine (Table IV). However, the efficacy of moricizine approached that of encainide and flecainide when it was used as the first drug in patients with low left ventricular ejection fraction (<30 or <45%) or

as the second drug. Twelve of 20 patients who took moricizine as a second drug were assigned to it at the start of the follow-up phase (Table III).

The superior efficacy of encainide and flecainide was not associated with a higher frequency of adverse effects. Encainide and flecainide were similar to each other in their adverse effect profile and tended to have fewer adverse effects than imipramine, moricizine or placebo (Tables IV to VI). No drug was different from placebo with respect to heart failure, but flecainide had a slightly higher incidence of moderate to severe heart failure than encainide (Figure 2). Considering the multiple comparisons, the latter difference was not statistically significant. Whether this finding has clinical significance is uncertain. Previous studies have shown that flecainide can aggravate heart failure, particularly in patients in New York Heart Association functional classes III and IV and left ventricular ejection fraction <30%.[19] Overall, fewer than 5% of the patients had to stop the CAPS drug because of heart failure during drug and dose selection or follow-up phases. Other adverse effects tended to occur less frequently on drugs with class IC action than on drugs with class IA action. Thus, encainide and flecainide are not only effective for treating ventricular arrhythmias after AMI but also are safe and well tolerated.

Additional comments: Because of the exclusion criteria used in CAPS, one cannot extrapolate the results to the entire post-AMI population. CAPS excluded patients with ventricular tachycardia ≥10 complexes and left ventricular ejection fraction ≤20%. Aggravation of heart failure or proarrhythmia might occur more frequently in patients with left ventricular ejection fraction ≤20% or sustained ventricular tachycardia, were they exposed to these drugs.[19,20]

CAPS was the first trial to compare encainide and flecainide after AMI. These drugs had high efficacy rates and were well tolerated in the year after infarction. This finding is consistent with previous studies in other populations.[21-24] Currently, the use of antiarrhythmic drugs after AMI in asymptomatic patients is of unproven value. The Cardiac Arrhythmia Suppression Trial is assessing the ability of long-term suppression of ventricular arrhythmias after AMI to reduce the sudden cardiac death rate.

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Appendix—The Cardiac Arrhythmia Pilot Study Investigators

University of Alabama at Birmingham: Albert L. Waldo, MD*, William J. Rogers, MD*, Richard W. Henthorn, MD, Brian Olshansky, MD, Andrew E. Epstein, MD, Albert Oberman, MD, Mark D. Cohen, MD, Paul Hess, MD, Coordinators: Donna Kerns, RN, Terry Glickman, RN.

Baylor College of Medicine: Craig M. Pratt, MD*, J. Alan Herd, MD, Christopher R. Wyndham, MD, Allen Seals, MD, Miguel Quinones, MD, Robert Roberts, MD, Mario Verani, MD, James Young, MD, Coordinators: Amy Galloway, RN, Ann Riordan, RN, Pat Carlson, RN, Beth C. Thornton, RN.

Brown University Affiliated Hospitals: Robert J. Capone, MD*, Edward W. Bough, MD, David Ahern, PhD, Michael Follick, PhD, Larry Gorkin, PhD, Abdul H. Khan, MD, Suh-Dong Hahn, MD, Henry Gerwitz, MD, Gregory Macina, MD, Gary Heller, MD, Richard Carleton, MD, Coordinators: Kathryn Alberti, RN,

Connie Lamore, RN, Denise Tremblay, RN.

Columbia University: J. Thomas Bigger, Jr., MD*, James Coromilas, MD, Francis M. Weld, MD, Elsa-Grace V. Giardina, MD, James A. Reiffel, MD, Donald Kornfeld, MD, Jean Warner, MD, Alan Saroff, MD, Lynne L. Johnson, MD, Richard Sloan, PhD, Coordinator: Robert Stanyon, RN.

Johns Hopkins University: Lawrence S. Griffith, MD*, Philip R. Reid, MD*, Edward V. Platia, MD, Craig Ewart, PhD, Diane Becker, PhD, Bernard Tabaznik, MD, Stephen Pollock, MD, Jeffrey Quartner, MD, Dean Taylor, MD, Michael Keleman, MD, Sheldon Gottlieb, MD, Morton Mower, MD, Michael Mirowski, MD, Nisha Chandra, MD, Raymond Bahr, MD, Coordinators; Patricia Pollock RN, Linda Prinkey, RN, Mary Sullivan, RN, Diana Aarons, RN, Carol Williams, RN.

Medical College of Virginia: David W. Richardson, MD*, Donald W. Romhilt, MD, Andrea Hastillo, MD, Fred D. Robinson, MD, John Herre, MD, Coordinator: Barbara Bane.

Montreal Heart Institute: Pierre A. Theroux, MD*, Denis Roy, MD, Coordinator: Doris Morissette, RN.

University of Rochester: Toshio Akiyama, MD*, William B. Hood, Jr., MD, Paul N. Yu, MD, William Henion, MD, Gur Adhar, MD, Mark Rosenzweig, MD, James Doling, MD, Robert Easley, MD, Coordinators: Laura Butler, Marcia Keller, RN.

Salt Lake City Research Foundation: Allan H. Barker, MD*, Jeffrey L. Anderson, MD, Robert E. Fowles, MD, Coordinators: Ellen N. Doran, Joan R. Lutz, RN.

Vanderbilt University: Raymond L. Woosley, MD, PhD*, Dan M. Roden, MD, Toby Barbey, MD, Bart Campbell, MD, Kathy Thompson, MD, Lyle Siddoway, MD, Debbie Echt, MD, John T. Lee, MD, Coordinators: Mary DeLoache, RN, MSN, Tina Thomas, RN, Leslie Jared, RN, MSN, Laurie Hays, RN.

Coordinating Center, University of Washington, Seattle: Alfred Hallstrom, PhD*, Mary Jo Gillespie, MS, Leon Greene, MD, Margit Scholz.

Project Office, National Heart, Lung, and Blood Institute, Bethesda: Lawrence Friedman, MD*, C. Eugene Harris, Eleanor Schron, RN, MS, Joel Verter, PhD, Salim Yusuf, MD.

Drug Distribution Center, VA Cooperative Studies Clinical Research Pharmacy Coordinating Center, Alburquerque: Dennis Toussaint, RPh, MS, Clair Haakenson, RPh, MS.

Ambulatory Electrocardiogram Reading Center: Clinical Data, Inc., Boston, Israel M. Stein, MD*, Carolyn O'Connor.

Steering Committee Chairman: J. Thomas Bigger, Jr., MD.

Safety and Data Monitoring Board: J. David Bristow, MD (Chairman), David DeMets, PhD, Charles Fisch, MD, Alan S. Nies, MD, Jeremy N. Ruskin, MD, Harold C. Strauss, MD, Leroy Walters, PhD.

* Principal investigator.

Adoption of Thrombolytic Therapy in the Management of Acute Myocardial Infarction

MARK A. HLATKY, MD, HARRY COTUGNO, PhD, CHRISTOPHER O'CONNOR, MD, DANIEL B. MARK, MD, MPH, DAVID B. PRYOR, MD, and ROBERT M. CALIFF, MD

A national survey of 1,065 physicians was carried out to document current use of thrombolytic therapy for acute myocardial infarction (AMI). In early 1987, thrombolytic therapy was used by 66% of respondents. Among those who used thrombolytic therapy, 92% used streptokinase, 13% used tissue-type plasminogen activator and 3% used urokinase. Most (72%) used intravenous administration exclusively and only 5% used intracoronary administration exclusively. Despite widespread acceptance of thrombolytic therapy, most physicians gave it to <25% of their patients. Duration of symptoms was rated as the single most important factor affecting the decision to use thrombolytic therapy; 45% had a time limit of <4 hours and 85% had a time limit of <6 hours. Complications of AMI and electrocardiographic findings were factors also considered in the decision to give this therapy. A physician's adoption of thrombolytic therapy was significantly associated with several characteristics: specialty type, number of AMI patients treated, physician age and access to cardiac catheterization. In addition, physicians using thrombolytic therapy had a significantly different use of medications and laboratory tests for all patients with AMI. This survey documents rapid acceptance of thrombolytic therapy for AMI, particularly in patients with short duration of symptoms or evidence of high risk.

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A radical change has occurred over the past decade in the approach to patients with acute myocardial infarction (AMI). In 1980, DeWood et al[1] showed that acute coronary thrombosis can be identified angiographically in most patients with AMI. This observation was quickly followed by a flurry of reports demonstrating that lysis of the coronary thrombus could be achieved by intracoronary infusion of streptokinase.[2–4] Other studies demonstrated the efficacy of intravenous streptokinase[5] and tissue-type plasminogen activator (t-PA) in lysing coronary thrombi,[6,7] and subsequent research suggested that such therapy may salvage myocardium and reduce mortality.[8–11] The impact of thrombolytic therapy upon the care of patients with AMI by practicing physicians remains uncertain. This study documents current patterns of use of thrombolytic therapy for AMI and examines the process by which such therapeutic innovations are adopted into practice.

From the Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina, and the Gallup Organization, Inc., Princeton, New Jersey. This study was supported in part by a grant from SmithKline Consumer Products, Philadelphia, Pennsylvania; grants HS-04873 and HS-05635 from the National Center for Health Services Research, Rockville, Maryland; grant HL-36587 from the National Heart, Lung and Blood Institute, Bethesda, Maryland; and grants from the Andrew W. Mellon Foundation, New York, New York; and the Robert Wood Johnson Foundation, Princeton, New Jersey. Manuscript received August 27, 1987; revised manuscript received and accepted November 13, 1987.

Address for reprints: Mark A. Hlatky, MD, Box 31265, Duke University Medical Center, Durham, North Carolina 27710.

Methods

The methods of this study have been described in detail elsewhere.[12] Briefly, a self-administered questionnaire regarding management of AMI was prepared that included items concerning thrombolytic therapy as well as items previously used in a 1979 survey of physician practice in the management of uncomplicated AMI.[13] The questionnaire was mailed by the Gallup Organization in January 1987 to cardiologists, internists and family and general practitioners randomly chosen from the American Medical Association's Physician Masterfile. Usable responses were received from 1,065 physicians, 21% of those contacted.

Completed questionnaires were entered into computer storage and checked for accuracy and completeness by the Gallup Organization. Data were subsequently transferred to Duke University Medical Center for analysis using SAS statistical software. Dif-

ferences in discrete valued variables were assessed for statistical significance using chi-square tests and differences in ordered and continuous variables by Wilcoxon rank-sum tests. Multivariable analyses of factors related to the adoption of thrombolytic therapy were performed using multiple logistic regression.

Results

In 1980, only 2% of respondents used thrombolytic therapy to treat patients with AMI, whereas by 1985 their number rose to 50% and by 1987 to 66% (Figure 1A). In early 1987, 92% of physicians administering thrombolytic therapy for AMI used streptokinase, 13% used tissue-type plasminogen activator (t-PA) and 3% used urokinase (these figures total >100% because some physicians used more than 1 agent). Most respondents (72%) used the intravenous route exclusively, 5% used the intracoronary route exclusively, 19% used either route and the remaining 4% did not specify a route of administration.

Respondents rated several factors as either "very important," "somewhat important," "not too important," and "not at all important" in their decision to give a patient thrombolytic therapy (Table I). Duration of pain was the single most important factor in this decision, and 4 to 6 hours was the general time limit beyond which the physician would not give thrombolytic therapy (Figure 2). Ongoing pain was also a key factor in this decision, as were specific complications of AMI such as hypotension and ventricular tachycardia or fibrillation. Electrocardiographic factors such as site of infarction, presence of Q waves and height and extent of ST-segment elevation were considered in the decision to use thrombolytic therapy, but were not of decisive importance. Finally, the patient's age was clearly a factor, whereas the patient's sex was not.

Despite widespread acceptance of thrombolytic therapy for AMI, respondents who used this therapy gave it only to a minority of their patients. Most respondents (58%) used thrombolytic therapy in less than one-quarter of their patients with AMI, 25% used it in one-quarter to one-half, and only 17% used it in more than half of their patients. In order to explore whether stringent patient selection criteria were responsible for the low proportion of AMI patients given thrombolytic therapy, we formed a "selectivity index" by counting the number of factors from Table I that a physician rated as "very important" in the decision to give thrombolytic therapy. There was no significant correlation between a physician's "selectivity index" and the proportion of his patients with AMI given thrombolytic therapy (Spearman correlation coefficient = −0.05, p = 0.22). In contrast, physicians who accepted a longer time interval between onset of symptoms and administration of the thrombolytic agent treated a significantly greater proportion of their AMI patients with thrombolytic therapy (Spearman correlation coefficient = +0.10, p = 0.0085).

Coronary angiography was generally recommended (73%) for patients with uncomplicated AMI given thrombolytic therapy. Very few physicians, however, recommended cardiac catheterization immediately

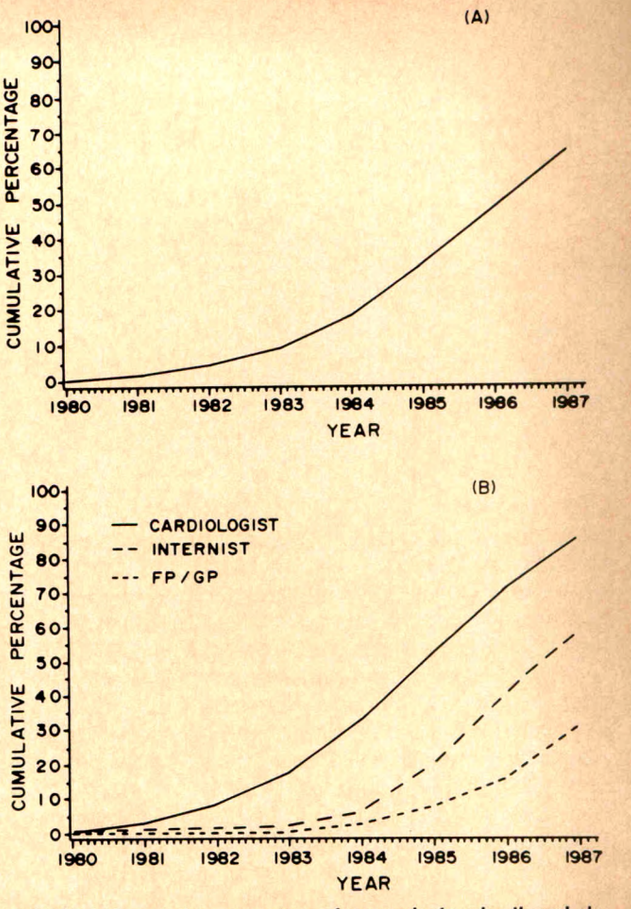

FIGURE 1. Cumulative percentage of respondents using thrombolytic therapy in various calendar years. The top panel shows the data from all respondents (*A*), and the bottom panel shows data according to physician specialty type (*B*). FP/GP = family practice or general practice.

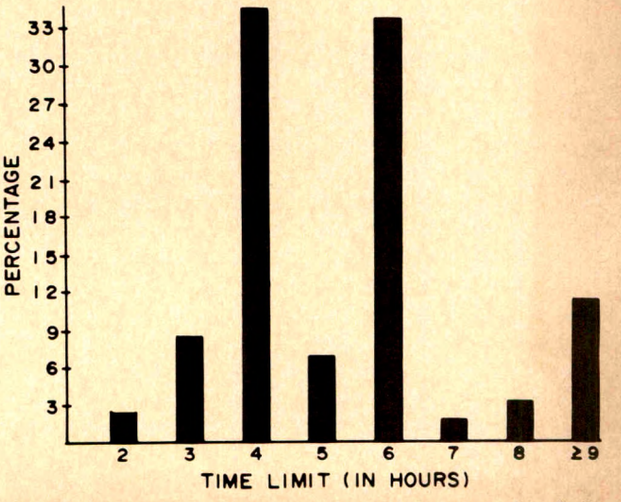

FIGURE 2. Percentage of respondents who set various time limits between the onset of symptoms and administration of thrombolytic therapy.

TABLE I Factors Affecting the Decision to Use Thrombolytic Therapy (n = 1,065)

Factor	Very Important (%)	Somewhat Important (%)	Not Too Important (%)	Not at All Important (%)
Duration of pain	78	16	4	2
Continuing pain	57	30	10	3
Hypotension or shock	53	36	8	3
Age (yrs)	40	45	12	3
VT/VF	33	36	23	8
Anterior vs inferior AMI	28	43	19	10
Presence of Q waves	23	43	23	11
Height of ST elevation	23	35	29	13
Number of leads with ST elevation	20	41	27	12
History of prior AMI	15	44	28	13
Reciprocal ST depression	9	30	41	20
Patient's sex	1	8	30	61

AMI = acute myocardial infarction; VT/VF = ventricular tachycardia or fibrillation.

TABLE II Use of Thrombolytic Therapy Among Various Groups of Physicians (n = 1,065)

	Percentage Using Thrombolytic Therapy	p Value
Specialty		<0.0001
Cardiologist	86	
Internist	60	
FP/GP	33	
Year of MD degree		<0.0001
≤1970	57	
≥1971	73	
Practice type		0.016
Private	64	
Nonprivate	71	
Group size		<0.0001
Solo	52	
<5	66	
≥5	73	
AMI patients per year		<0.0001
≤10	35	
11–25	69	
26–50	85	
>50	93	
Cardiac catheterization		<0.0001
Available	76	
Not available	53	

AMI = acute myocardial infarction; FP/GP = family or general practitioner.

TABLE III Percentage of Physicians Routinely Using Various Medications, According to Their Use of Thrombolytic Therapy (n = 1,065)

	Thrombolytic Therapy User		
	Yes (%)	No (%)	p Value
In-hospital			
Aspirin	64	47	<0.0001
Dipyridamole	21	21	1.0
Heparin/warfarin	13	9	0.04
β-blockers (IV)	17	8	<0.0001
β-blockers (PO)	81	57	<0.0001
Calcium antagonists	43	33	0.001
Digitalis	1	4	<0.0001
Antiarrhythmics	33	32	0.79
After discharge			
Aspirin	88	71	<0.0001
Dipyridamole	27	28	0.67
Warfarin	2	3	0.28
β-blockers	85	65	<0.0001
Calcium antagonists	41	34	0.02
Digitalis	1	3	0.03
Antiarrhythmics	2	7	<0.0001
Lipid-lowering drugs	10	16	0.009

IV = intravenous administration; PO = oral administration.

upon hospital admission. Specifically, only 13% of physicians who used thrombolytic therapy and who had cardiac catheterization facilities in their hospital routinely recommended coronary angiography immediately on admission for patients with AMI.

Therapy acceptance: Thrombolytic therapy was adopted relatively early after its introduction by some physicians, and much later or not at all by others. Several physician characteristics were significantly correlated with the time at which he began to use thrombolytic therapy. Specialty type was the single most important factor (Figure 1B): cardiologists generally adopted thrombolytic therapy. first, followed roughly 2 years later by internists and 2 years after that by family and general practitioners ($p < 0.0001$). Therapy adoption was also significantly affected by physician age, private practice, group practice size, volume of AMI patients and availability of cardiac catheterization (Table II).

Multivariable logistic regression analysis revealed that the independent factors affecting physician acceptance of thrombolytic therapy were specialty ($p < 0.0001$), number of patients with AMI treated in 1986 ($p < 0.0001$), physician age ($p < 0.0001$), and availability of a cardiac catheterization laboratory in the physician's hospital ($p = 0.008$). After accounting for these factors, the size of the physician's practice group and whether the physician was in private practice had no independent effect on the likelihood of using thrombolytic therapy.

Practice style and thrombolytic therapy: In addition to questions about thrombolytic therapy, the survey contained questions about the general manage-

ment of patients with uncomplicated AMI. We examined these responses in detail to determine whether the physicians who used thrombolytic therapy had a distinct practice style with regard to patients with AMI. Physicians who used thrombolytic therapy gave a significantly different set of medications to *all* their patients with AMI (Table III). Physicians who used thrombolytic therapy were more likely to use aspirin routinely in all patients with AMI, both during the initial hospitalization and after discharge. They also were significantly more likely to use β blockers and calcium antagonists and significantly less likely to use digitalis, prophylactic antiarrhythmics and lipid-lowering drugs routinely in patients with AMI.

Physicians using thrombolytic therapy also employed a significantly different predischarge evaluation for *all* their patients with AMI (Table IV). Exercise electrocardiography was recommended by >90% of such physicians and cardiac catheterization also was recommended more frequently, especially in patients with positive exercise tests or non-Q-wave AMIs. Physicians using thrombolytic therapy were more likely to use 24-hour ambulatory monitoring, resting radionuclide angiography and exercise thallium scintigraphy, although these tests were not used routinely by most physicians.

TABLE IV Percentage of Physicians Using Various Predischarge Laboratory Tests, According to Their Use of Thrombolytic Therapy (n = 1,065)

Test	Thrombolytic Therapy User		p Value
	Yes (%)	No (%)	
Exercise electrocardiogram	91	68	<0.0001
Cardiac catheterization for positive exercise electrocardiogram	91	68	<0.0001
Cardiac catheterization for non-Q-wave AMI	79	63	<0.0001
Ambulatory electrocardiogram	44	29	<0.0001
Rest radionuclide angiogram	18	11	0.006
Exercise radionuclide angiogram	8	8	0.89
Exercise thallium scintigram	17	11	0.01

AMI = acute myocardial infarction.

Discussion

This study demonstrates that thrombolytic therapy is now widely accepted in the management of AMI. The most common method of thrombolysis in early 1987 was the administration of intravenous streptokinase, typically in the dose of 1.5 million units. Intracoronary administration of thrombolytic agents was generally not employed in the treatment of AMI, even by physicians with cardiac catheterization facilities available in their hospital. Thus, although intracoronary administration was crucial in gaining acceptance of the thrombolytic therapy for AMI, the advantages of the intravenous route in rapidity and ease of administration have apparently left few using the intracoronary route. Thrombolytic agents other than streptokinase were not frequently used in early 1987, but the results from ongoing trials[7] suggest that tissue-type plasminogen activator (t-PA) use will increase now that this drug has been approved by the Food and Drug Administration.

Physicians considered many factors in their decision to give thrombolytic therapy to a patient with AMI (Table I), the single most important factor being the duration of the patient's symptoms. Most physicians (85%) would not give thrombolytic therapy >6 hours after onset of symptoms (Figure 2). Because the location of the AMI and the presence of complications such as hypotension, shock or ventricular fibrillation were rated as very important factors in the decision to use thrombolytic therapy, the data also suggest that physicians were reserving it for more severely affected patients.

One striking finding was that despite the widespread acceptance of thrombolytic therapy, most physicians gave it to <25% of their patients. Our data suggest that the main reason may be the stringent time limits physicians place on the interval between symptom onset and drug administration. Although physicians clearly considered many factors in the decision to give a patient thrombolytic therapy (Table I), only the time limit a physician placed on the duration of symptoms was significantly correlated with the proportion of patients treated. These findings suggest that most AMI patients will be treated with thrombolytic therapy only if the sources of treatment delay can be identified and eliminated.

Thrombolytic therapy has been adopted primarily by the physicians who treat the most patients with AMI, and by younger physicians. In addition, physicians in the hospitals with facilities to perform cardiac catheterization were more likely to adopt this therapy. Because most physicians do not generally use emergency coronary angiography, this finding may reflect an overall more aggressive approach toward coronary revascularatization in such hospitals.

Physicians who used thrombolytic therapy also appear to have a distinctly different management style for all AMI patients. Specifically, they use β blockers, platelet active drugs such as aspirin and calcium antagonists more frequently (Table III). Furthermore, they were also more likely to use exercise testing and cardiac catheterization in patients with AMI (Table IV), presumably in an attempt to document residual jeopardized myocardium suitable for revascularization procedures. Due to the wording of the questions in this survey, the data in Tables III and IV refer to the physicians' management approach to *all* of their AMI patients, not just to the patients treated with thrombolytic therapy. Thus, the data in Table III indicate that 17% of physicians who use thrombolytic therapy administer intravenous β blockers routinely to all their AMI patients, and *not* that 17% of patients given thrombolytic therapy are given intravenous β blockers. Despite this limitation of the data, it appears that users of thrombolytic therapy have a more aggressive overall approach to the management of AMI patients, including a more extensive use of both medications and laboratory testing.

This study had a number of other important limitations. First, it was a survey of how physicians say they practice, rather than an actual audit of their practices. Second, many physicians did not participate in the study. Because nonrespondents may differ from respondents in a variety of ways, our results must be interpreted with caution. In particular, although a stratified random sample of physicians across the U.S. was used in this survey, the possibility of nonresponse bias must be considered in any extrapolation of these results to national estimates.

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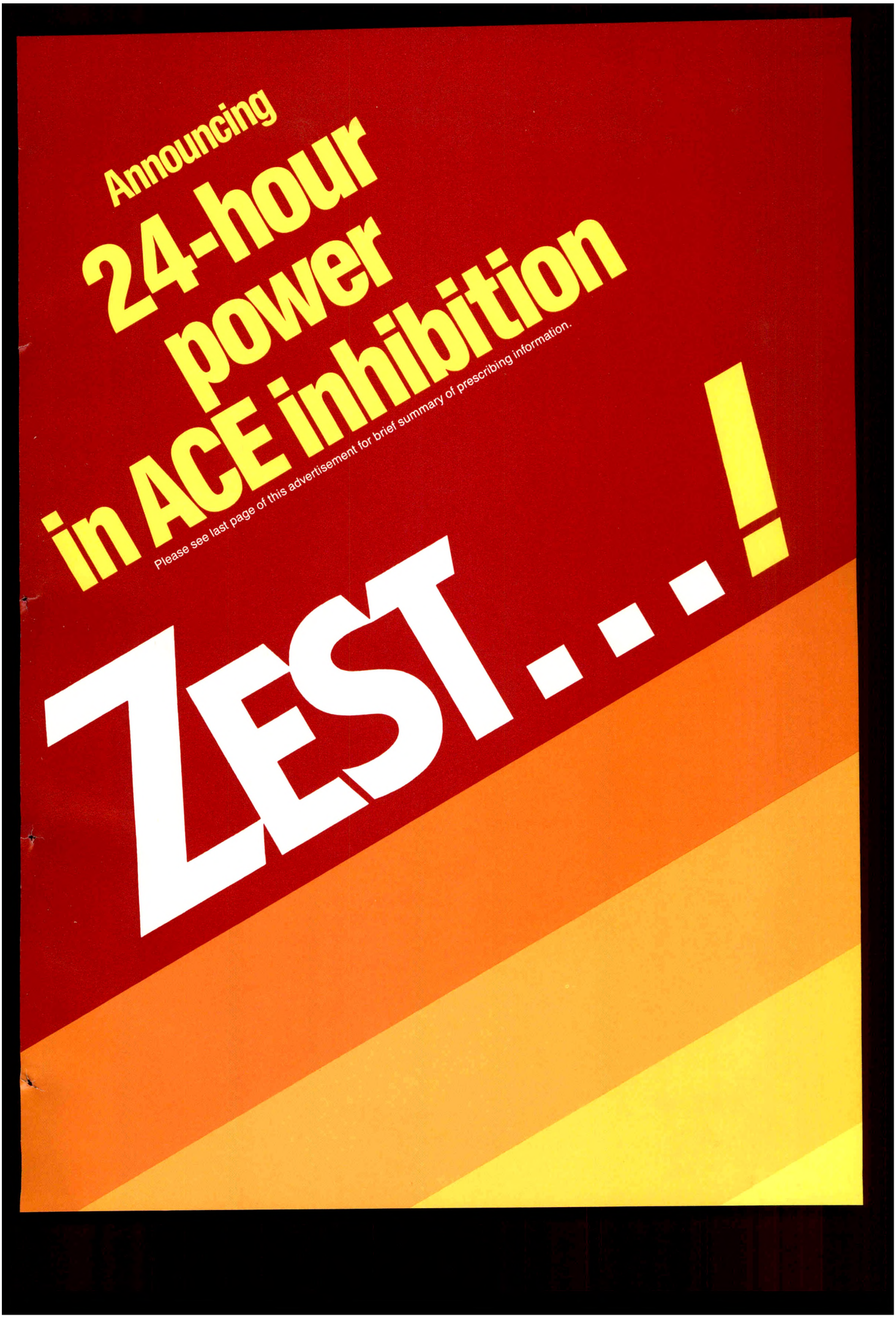
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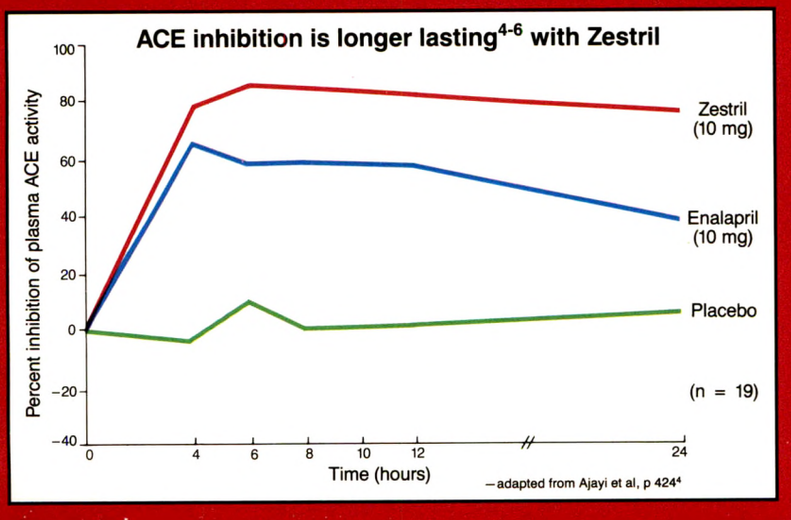
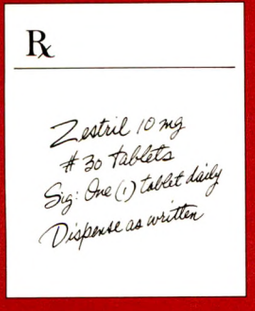
Zestril: The longest-acting ACE inhibitor for treating hypertension

Zestril assures 24-hour blood pressure control with a half-life of almost 13 hours.[1] That's longer than that of either enalapril[2] or captopril.[3] So angiotensin converting enzyme (ACE) inhibition with Zestril is longer lasting than enalapril—sustained 24 hours after a single dose.[4-6]



Zestril: Hypertensive patients start and stay at one tablet a day

A single tablet of Zestril controls blood pressure for a full 24 hours[7]—unlike other ACE inhibitors, which may have to be increased to b.i.d.[2] or t.i.d.[3] dosing in some patients. The predictable once-daily dosage of Zestril enhances patient compliance and cost effectiveness.



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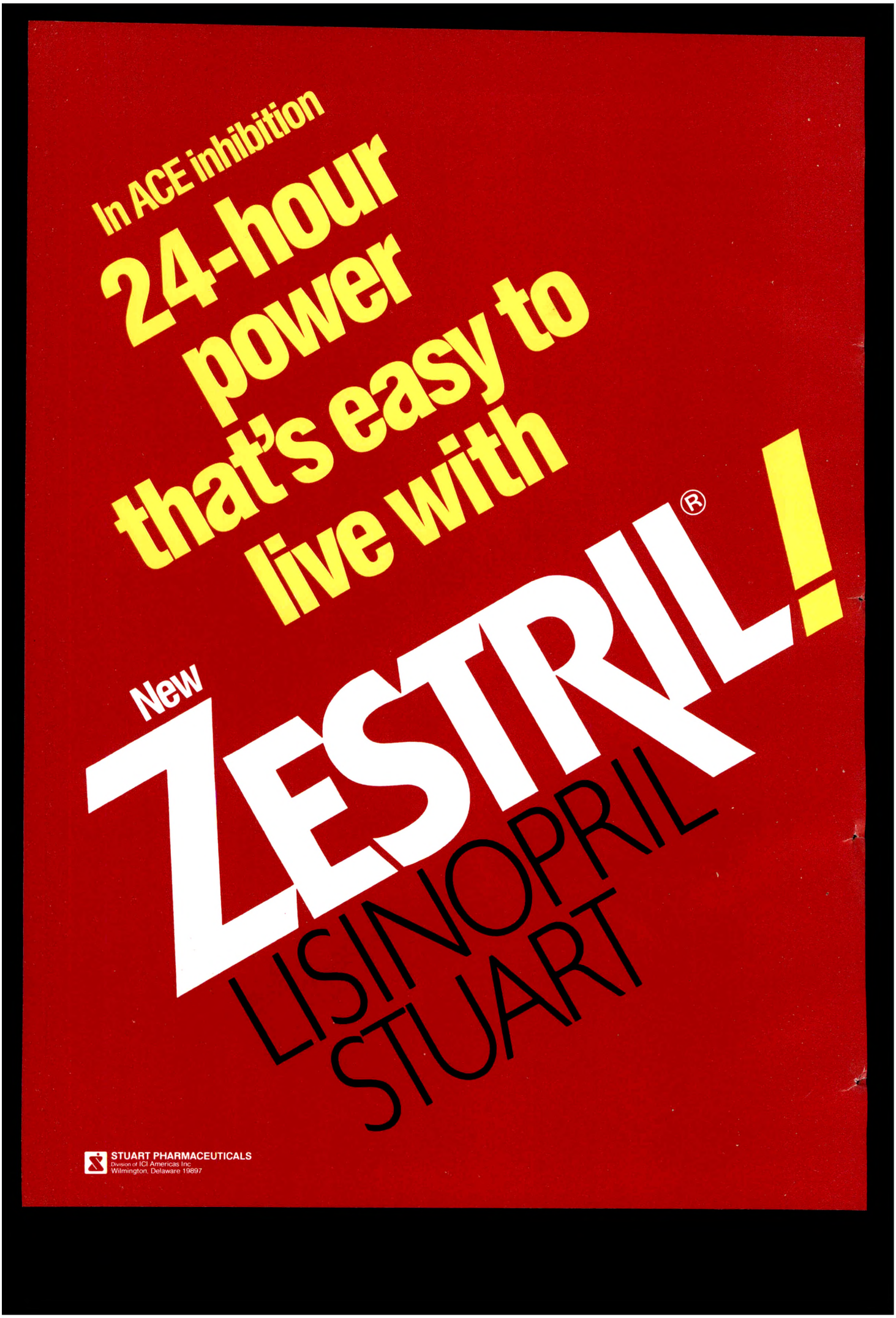
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Zestril: 24-hour blood pressure control without reliance on metabolism

Zestril provides complete 24-hour control without reliance on liver metabolism.[8] It does not require bioactivation[8]—as needed with the prodrug enalapril.[2,8] Absorption is unaffected by food.[9]

Zestril: 24-hour blood pressure control that's well tolerated

Zestril achieves 24-hour control with a low incidence of side effects. It is a nonsulfhydryl-containing drug. That's why rash and/or taste disturbance sometimes associated with the sulfhydryl-containing drug captopril[10] are rarely seen with Zestril. In Zestril clinical trials, the most frequently reported side effects were as follows:

Side Effects	Zestril (n = 2,003*)	—	Placebo (n = 207)
Dizziness	6.3%	—	1.9%
Headache	5.3%	—	1.9%
Fatigue	3.3%	—	1.0%
Diarrhea	3.2%	—	2.4%
Upper respiratory symptoms	3.0%	—	0.0%
Cough	2.9%	—	1.0%

*Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

- Only 6% of patients discontinued therapy in controlled clinical trials.
- Symptomatic hypotension occurs infrequently (0.8%) in patients with normal renal function.

Zestril dosage in hypertension
Starting dose is 10 mg once a day. Usual dosage range for maintenance: 20 to 40 mg per day, administered in a single daily dose.

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INDICATIONS AND USAGE. Zestril is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents. In using Zestril, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that Zestril does not have a similar risk. (See WARNINGS.) **CONTRAINDICATIONS.** Zestril is contraindicated in patients who are hypersensitive to this product. **WARNINGS. Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including Zestril. In such cases, Zestril should be promptly discontinued, and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, eg, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered. (See ADVERSE REACTIONS.) Hypotension:** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of use with Zestril in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of Zestril and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. **Neutropenia/Agranulocytosis:** Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of Zestril are insufficient to show that Zestril does not cause agranulocytosis at similar rates. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered. **PRECAUTIONS. General. Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including Zestril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of Zestril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when Zestril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of Zestril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.) Hyperkalemia:** In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with Zestril. (See Drug Interactions.) **Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Zestril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion. **Information for Patients. Angioedema:** Angioedema, including laryngeal edema, may occur especially following the first dose of Zestril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician. **Symptomatic Hypotension:** Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician. **Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician. **Neutropenia:** Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which may be a sign of neutropenia. **NOTE:** As with many other drugs, certain advice to patients being treated with Zestril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. **Drug Interactions. Hypotension – Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Zestril. The possibility of hypotensive effects with Zestril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Zestril. If it is necessary to continue the diuretic, initiate therapy with Zestril at a dose of 5 mg daily, and provide medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving Zestril, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.) **Indomethacin:** In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of Zestril alone were compared to Zestril given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant. **Other Agents:** Zestril has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when Zestril was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of Zestril. **Agents Increasing Serum Potassium:** Zestril attenuates potassium loss caused by thiazide-type diuretics. Use of Zestril with potassium-sparing diuretics (eg, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 times* the maximum recommended daily human dose) or when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). *Based on patient weight of 50 Kg. Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow. There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. **Pregnancy. Pregnancy Category C:** Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1,000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1,000 mg/kg this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation. Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man. Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at a dose of lisinopril at 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). By whole body autoradiography, radioactivity was found in the placenta following administration of labeled lisinopril to pregnant rats, but none was found in the fetuses. There are no adequate and well-controlled studies in pregnant women. Zestril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. It is not known whether this drug is excreted in human milk.

ZESTRIL® (lisinopril)

Because many drugs are excreted in human milk, caution should be exercised when Zestril is given to a nursing mother. **Pediatric Use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS.** Zestril has been found to be generally well tolerated in controlled clinical trials involving 2003 patients and subjects. The most frequent clinical adverse experiences in controlled trials were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range. For adverse experiences which occurred in more than 1% of patients and subjects treated with Zestril or Zestril plus hydrochlorothiazide in controlled clinical trials, comparative incidence data are listed in the table below.

Percent of Patients in Controlled Studies

	Zestril (n = 2003†) Incidence (discontinuation)	Zestril/Hydrochlorothiazide (n = 644) Incidence (discontinuation)	Placebo (n = 207) Incidence
Dizziness	6.3 (0.6)	9.0 (0.9)	1.9
Headache	5.3 (0.2)	4.3 (0.5)	1.9
Fatigue	3.3 (0.2)	3.9 (0.5)	1.0
Diarrhea	3.2 (0.3)	2.6 (0.3)	2.4
Upper Respiratory Symptoms	3.0 (0.0)	4.5 (0.0)	0.0
Cough	2.9 (0.4)	4.5 (0.8)	1.0
Nausea	2.3 (0.3)	2.5 (0.2)	2.4
Hypotension	1.8 (0.8)	1.6 (0.5)	0.5
Rash	1.5 (0.4)	1.6 (0.2)	0.5
Orthostatic Effects	1.4 (0.0)	3.4 (0.2)	1.0
Asthenia	1.3 (0.4)	2.0 (0.2)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.0)	0.5
Dyspnea	1.1 (0.0)	0.5 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.0
Paresthesia	0.8 (0.0)	2.0 (0.2)	0.0
Impotence	0.7 (0.2)	1.6 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.8 (0.6)	0.5
Back Pain	0.5 (0.0)	1.1 (0.0)	1.4
Nasal Congestion	0.3 (0.0)	1.2 (0.0)	0.0
Decreased Libido	0.2 (0.1)	1.2 (0.0)	0.0
Vertigo	0.1 (0.0)	1.1 (0.2)	0.0

†Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in the controlled trials and rarer, serious, possibly drug related events reported in uncontrolled studies or marketing experience included: BODY AS A WHOLE: Chest discomfort, fever, flushing. CARDIOVASCULAR: Angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, palpitation. DIGESTIVE: Abdominal pain, anorexia, constipation, flatulence. METABOLISM: Gout. MUSCULOSKELETAL: Joint pain, shoulder pain. NERVOUS SYSTEM/PSYCHIATRIC: Depression, somnolence, insomnia, stroke. RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain. UROGENITAL: Oliguria, progressive azotemia, acute renal failure. OTHER: Blurred vision, pruritus, urinary tract infection, vasculitis of the legs. ANGIOEDEMA: Angioedema has been reported in patients receiving Zestril (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with Zestril should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.) HYPOTENSION: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. (See WARNINGS.) In patients with congestive heart failure, hypotension occurred in 5.0% and syncope occurred in 1.0% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients. **Clinical Laboratory Test Findings. Serum Electrolytes:** Hyperkalemia (See PRECAUTIONS.) **Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with Zestril alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased. **Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with Zestril but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. **Other (Causal Relationship Unknown):** Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%), and serum potassium (0.4%). **OVERDOSAGE.** The oral LD_{50} of lisinopril is greater than 20 g/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. **DOSAGE AND ADMINISTRATION. Initial Therapy:** In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20-40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with Zestril alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of Zestril. **Diuretic Treated Patients:** In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of Zestril. The diuretic should be discontinued, if possible, for two or three days before beginning therapy with Zestril to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of Zestril should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with Zestril alone, diuretic therapy may be resumed as described above. If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) Concomitant administration of Zestril with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.) **Use in Elderly:** In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of Zestril. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution. **Dosage Adjustment in Renal Impairment:** The usual dose of Zestril (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance > 10 mL/min ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine-Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	>30	10
Moderate to Severe Impairment	≥10 ≤30	5
Dialysis Patients	<10	2.5‡

‡Dosage or dosing interval should be adjusted depending on the blood pressure response. Rev E 12/87

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Trends in Physician Management of Uncomplicated Acute Myocardial Infarction, 1970 to 1987

MARK A. HLATKY, MD, HARRY E. COTUGNO, PhD, DANIEL B. MARK, MD, MPH, CHRISTOPHER O'CONNOR, MD, ROBERT M. CALIFF, MD, and DAVID B. PRYOR, MD

To document current management of uncomplicated acute myocardial infarction (AMI), a national survey of 1,065 physicians was performed. Items from previous surveys in 1970 and 1979 were included to permit analysis of time trends in management. Median hospital stay dropped from 21 days in 1970 to 9 days in 1987. Use of β blockers and aspirin doubled between 1979 and 1987, while use of anticoagulation and sulfinpyrazone dropped 4- to 10-fold. In 1987, coronary angiography was used commonly, especially in younger patients or those with either a non-Q-wave AMI, intravenous thrombolytic therapy or a positive exercise test. These findings document the increasingly aggressive approach to the management of patients with uncomplicated AMI.

(Am J Cardiol 1988;61:515–518)

Acute myocardial infarction (AMI) is a common and serious illness that accounts for 500,000 deaths annually in the U.S. Management of AMI thus represents an important aspect of medical practice with far-reaching implications in terms of both lives and dollars.

Physician practice in treating uncomplicated AMI was surveyed in 1970 and again in 1979 under the auspices of the American Heart Association.[1,2] Comparison of the results of these 2 surveys documented considerable evolution in the management approach toward AMI between 1970 and 1979. Further advances have been made since the 1979 survey in evaluation and therapy of the AMI patient, but the extent to which these advances in knowledge have been incorporated into practice is uncertain. This study assesses quantitatively current physician practice in the management of AMI and documents the acceptance of new strategies for the evaluation and treatment of AMI.

From the Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina, and the Gallup Organization, Inc., Princeton, New Jersey. This study was supported in part by a grant from SmithKline Consumer Products, Philadelphia, Pennsylvania; grants HS-04873 and HS-05635 from the National Center for Health Services Research, Rockville, Maryland; grant HL-36587 from the National Health, Lung and Blood Institute, Bethesda, Maryland; and grants from the Andrew W. Mellon Foundation, New York, New York; and the Robert Wood Johnson Foundation, Princeton, New Jersey. Manuscript received August 24, 1987; revised manuscript received and accepted November 9, 1987.

Address for reprints: Mark A. Hlatky, MD, Box 31265, Duke University Medical Center, Durham, North Carolina 27710.

Methods

A self-administered questionnaire was prepared that included items previously used in the 1979 survey,[2] as well as new items that reflected recent developments in management of AMI. The survey instrument was then pre-tested by the Gallup Organization in a sample of 100 physicians, and revised for clarity and ease of administration.

Questionnaires were mailed in January 1987 to 1,700 cardiologists, 1,700 internists, and 1,700 family and general practitioners randomly chosen from the American Medical Association's Physician Masterfile. A follow-up mailing was sent to all nonrespondents in February 1987, and a third mailing was sent to nonresponding cardiologists in March 1987. A total of 267 questionnaires were undeliverable because the physician had moved, 32 were returned by physicians who had retired from practice, 14 were returned blank and 17 were not usable. Usable responses were received from 1,065 physicians (21%). When telephone follow-up to 100 nonrespondents inquired about the reasons for not participating, most indicated they were too busy or had no interest in responding to surveys.

Completed questionnaires were entered into computer storage and checked for accuracy and completeness by the Gallup Organization. Data were subsequently transferred to Duke University Medical Center for analysis using SAS statistical software.

Results

A total of 1,065 responses were received: 526 from cardiologists, 273 from internists and 266 from family and general practitioners. The majority of respondents

TABLE I Medications and Procedures Used Routinely During Hospitalization (%)

	Cardiologists			Internal Medicine			Family/General Practice		
	1970	1979	1987	1970	1979	1987	1970	1979	1987
Drugs									
Anticoagulant	73	49	13	69	41	8	70	40	11
Antiarrhythmic	19	32	29	19	25	32	27	27	39
Nitrates	—	57	63	—	57	71	—	60	73
Beta blocker (oral)	—	38	77	—	34	74	—	32	62
Beta blocker (IV)	—	—	16	—	—	11	—	—	12
Digitalis	—	1	1	—	3	2	—	7	5
Calcium antagonists	—	—	42	—	—	40	—	—	36
Aspirin	—	—	63	—	—	52	—	—	55
Dipyridamole	—	—	21	—	—	17	—	—	23
Sulfinpyrazone	—	—	1	—	—	1	—	—	1
Tests									
Lipid levels	—	—	90	—	—	84	—	—	81
Exercise ECG	—	83	90	—	59	81	—	59	73
Ambulatory ECG	—	49	48	—	29	36	—	22	25
Exercise thallium	—	5–12	18	—	5–12	11		5–12	14
Rest RNA	—	—	18	—	—	16	—	—	10
Exercise RNA	—	—	7	—	—	7	—	—	11

ECG = electrocardiogram; IV = intravenous; RNA = radionuclide ventriculography; — = not available.

TABLE II Use of Coronary Angiography for Uncomplicated Acute Myocardial Infarction in 1987

	Cardiologists	Internal Medicine	Family/General Practice
Non-Q-wave AMI	79	60	47
Anterior Q-wave AMI	51	51	48
Inferior Q-wave AMI	30	37	41
Age <45 years	86	84	72
Age 45 to 65 years	57	61	62
Age >65 years	18	23	23
After IV thrombolytic therapy	86	71	49
Positive exercise ECG	92	84	73
Poor exercise tolerance	71	65	56
Low ejection fraction	61	50	47
Frequent VPCs	38	41	36

AMI = acute myocardial infarction; VPCs = ventricular premature complexes; other abbreviations as in Table I.

TABLE III Regimens Routinely Prescribed After Hospital Discharge for Uncomplicated Acute Myocardial Infarction

	Cardiologists		Internal Medicine		Family/General Practice	
	1979	1987	1979	1987	1979	1987
Beta blocker	39	81	35	82	32	70
Aspirin	41	84	46	84	50	77
Dipyridamole	13	25	15	27	17	32
Sulfinpyrazone	16	1	11	1	10	1
Anticoagulants	6	2	10	2	14	4
Nitrates	59	59	59	66	60	70
Calcium antagonists	—	40	—	39	—	36
Digitalis	3	1	8	2	15	3
Antiarrhythmics	5	1	8	7	10	7
Stop smoking	97	96	97	93	96	89
Cholesterol-lowering diet	77	92	68	86	72	83
Lipid-lowering drugs	—	10	—	9	—	18
Exercise program	—	85	—	84	—	83

were in private community practice (62%), with the remainder in academic practice (12%), full-time hospital-based practices (9%), health maintenance organizations (3%), fellowship training (2%), with miscellaneous or unavailable practice setting data for the remaining respondents (12%). Half of the respondents graduated from medical school before 1975 and 42% of the respondents had managed 25 or more patients with AMI in the previous year.

As in the 1979 survey, "uncomplicated AMI" was defined in the cover letter as "without serious or recurrent arhythmia, persistent pain, shock, or congestive heart failure." The length of stay for patients with uncomplicated AMI decreased dramatically from 1970 to 1979, and again from 1979 to 1987. The median total hospital stay was 21 days in 1970, 14 days in 1979, and 9 days in 1987. The intensive care unit component of the hospital stay also decreased sharply: 4.5 days in 1970, 3.5 days in 1979, and 2.8 days in 1987.

Physicians were asked to define the drugs they usually prescribed during the hospital stay of patients with uncomplicated AMI and responses were contrasted with those obtained in 1970 and 1979 (Table I). Full-dose anticoagulation with intravenous heparin followed by oral warfarin decreased progressively from 1970 to 1987. Use of prophylactic antiarrhythmics increased from 1970 to 1979, but changed little from 1979 to 1987, with less than half of physicians using them routinely. β-blocker use during hospitalization increased markedly from 1979 to 1987, with 73% of respondents recommending oral agents and 14% using intravenous therapy. Calcium antagonists were not generally available in 1979, but by 1987 were widely used as part of the routine regimen for patients with AMI. In-hospital use of antiplatelet therapy was not

assessed in previous surveys, but in 1987 aspirin was used during hospitalization by over half the physicians and dipyridamole by 20%.

Trends in the predischarge evaluation of the patient with uncomplicated AMI are also summarized in Table I. A lipid panel and an exercise electrocardiogram were obtained by most physicians surveyed, while other predischarge tests were used much more selectively. Exercise test use has increased slightly since the 1979 survey and in 1987 was recommended for most patients with uncomplicated AMI. The use of 24-hour ambulatory electrocardiograms, however, changed little between 1979 and 1987, with the test used routinely by 39% of physicians surveyed. Radionuclide studies were seldom used routinely and have shown little change from 1979 to 1987; the exercise thallium scintigraphy in 1987 was used routinely by 15% of respondents, resting radionuclide ventriculography by 15%, and exercise radionuclide ventriculography by 8%.

The use of coronary angiography for patients with uncomplicated AMI was explored in some detail in the 1987 survey (Table II). When coronary angiography was used, it was generally recommended within 1 to 8 weeks after AMI, rather than in the early phases of infarction. In general, coronary angiography was more often recommended after non-Q-wave AMI than after Q-wave AMI and more often after anterior AMI than after inferior AMI (Table II). Angiography was recommended significantly more often for younger than for older patients. Furthermore, the percentage of younger patients recommended for angiography was much higher than in 1979, when roughly 50% of cardiologists and roughly 33% of internists and 33% of family and general practitioners recommended this procedure for patients younger than 45, whereas in the 1987 survey these figures had risen to 86%, 84% and 72%, respectively. Coronary angiography was usually recommended if the AMI had been treated with intravenous thrombolytic therapy or if there was evidence of residual ischemia on exercise testing.

The drugs usually prescribed for patients with uncomplicated AMI after hospital discharge are summarized in Table III. Data from the current survey are only compared with data from the 1979 survey, because 1970 data were not available. Advice to stop smoking has remained virtually universal and there has been a slight increase in the recommendation for a cholesterol-lowering diet between the 1979 and 1987 surveys. Routine use of β blockers, aspirin and dipyridamole after hospital discharge has essentially doubled between 1979 and 1987, with current β blocker and aspirin use at over 80% and dipyridamole at 25%. In contrast, routine use of sulfinpyrazone (Anturane) has dropped over 10-fold, and routine use of digitalis and anticoagulants has dropped 3-fold to 5-fold since 1979.

The patterns of β-blocker and aspirin use were examined in some detail in the current survey. Almost all respondents (over 80%) prescribed β blockers and aspirin to most patients after uncomplicated AMI in 1987. Of physicians who prescribe β blockers after myocardial infarction, in 1987 48% prescribed them indefinitely, 16% prescribed them for 2 to 3 years, 21% for 1 year and 10% for 6 months. Physicians who prescribed aspirin used relatively low doses: 40% used <325 mg/day, 42% used 325 mg/day and only 2% used >650 mg/day. Roughly 40% of cardiologists and a third of all respondents used enteric, safety-coated aspirin for most patients after uncomplicated AMI.

Physicians in 1987 allowed patients to resume usual activities even earlier after hospital discharge than they did in 1979 and 1970. Activities of relatively low metabolic cost, such as housework or a desk job, were permitted at a median of 6 weeks after uncomplicated AMI in 1987, compared with 8.5 weeks in 1970, and 6.5 to 7 weeks in 1979. Activities of higher metabolic cost, such as heavy labor or working in extremes of heat and cold, were in 1987 permitted at a median of 8 to 10 weeks, respectively, down from 13 to 17 weeks in 1970, and 12 to 13 weeks in 1979.

Discussion

This survey documents dramatic changes in physician management of uncomplicated AMI during the period 1970–1987. Patients are kept in intensive care and in the hospital roughly half as long and permitted to return to activities much sooner after hospital discharge. At the same time, the use of predischarge laboratory studies is much greater and drug treatment is much more aggressive.

Decades ago, long periods of bed rest were recommended for patients with AMI. The value of early mobilization was recognized in the 1940s and became commonly practiced in the 1950s,[3] with the feasibility of early hospital discharge demonstrated in the late 1960s and early 1970s.[4,5] As a result of these studies, the average patient with AMI in early 1987 was kept in the hospital for 9 days: a remarkable reduction from the average length of stay of 21 days in 1970. Further reductions in length of stay are under study, particularly for patients treated with thrombolytic therapy and immediate angioplasty.[6]

In-hospital regimens for the patient with AMI have also evolved considerably. The most dramatic change, the institution of thrombolytic therapy, is discussed in detail in a separate report.[7] β blockers have been used as secondary preventive measures and to reduce infarct size in the acute setting. Although most physicians begin oral β blockade in the hospital, only 14% use intravenous β-blocker therapy in the early stages of AMI. Despite the evidence from randomized studies suggesting a benefit of early intravenous therapy,[8] it appears that the intravenous use of β blockers in the acute phases remains less well accepted than the use of these agents in the recovery phases of AMI.

Risk stratification of the patient with AMI has been an area of considerable interest over the past decade. Exercise testing has been advocated as a valuable method of identifying the high-risk patient.[9] According to this survey, 83% of physicians routinely perform exercise testing for their patients with uncomplicated AMI. It has been proposed that risk stratification of the patient with AMI can be further refined by testing to document electrical instability and left ventricular dysfunction.[10] This survey indicated that most physi-

cians have remained selective in their use of 24-hour ambulatory monitoring, radionuclide ventriculography and thallium scintigraphy, recommending these procedures in less than half of their patients (Table I).

One clear trend documented in this survey was the widespread acceptance of coronary angiography in patients with uncomplicated AMI (Table II). Coronary angiography was more likely to be used in younger patients, with its use in patients <45 increasing considerably between 1979 and 1987. Coronary angiography was also recommended frequently in patients with jeopardized myocardium, such as those with positive exercise tests, previous intravenous thrombolytic therapy or a non-Q-wave AMI. These data suggest that physicians are attempting to identify patients for possible coronary revascularization. Due to space limitations, we were not able to explore the indications for coronary artery surgery or coronary angioplasty after uncomplicated AMI, but the available data suggested that most physicians have adopted an aggressive approach toward revascularization therapy.

Some of the largest shifts in practice documented in this survey were in the use of medications after hospital discharge. Routine use of β-adrenergic blocking agents rose from 35% in 1979 to almost 80% in early 1987. Furthermore, most physicians continue administering indefinitely β blockers to their patients. Several large randomized studies since 1979 have demonstrated that β blockers decrease mortality in patients after AMI.[8,11] Our findings suggest that these randomized studies have successfully modified the standard of practice across the U.S.

A surprising finding was that over 80% of respondents routinely recommend aspirin for patients after uncomplicated AMI, almost double the rate found in the 1979 survey. Since 1979, many studies have demonstrated the importance of thrombotic occlusion of a coronary artery in the etiology of AMI.[12] Two large randomized trials have demonstrated that low doses of aspirin prevent AMI and death in patients with unstable angina.[13,14] Several large randomized trials of aspirin after AMI failed to demonstrate statistically significant results individually, but when pooled they suggested a decrease in mortality in aspirin-treated patients after AMI. In view of this evidence, the Food and Drug Administration in 1985 approved use of aspirin as secondary prophylaxis for patients after AMI.[15] The results of this survey strongly suggest that aspirin has been accepted by most physicians for this indication.

One of the more interesting changes in practice is the virtual abandonment of sulfinpyrazone, which also has antiplatelet properties, as a secondary preventive agent after AMI. In 1979, almost 15% of physicians used sulfinpyrazone, but by 1987 only 1% were still using it. In 1978, a randomized trial published in a major journal reported a reduction in sudden cardiac death after AMI in patients treated with sulfinpyrazone.[16] Certain methods used in this study, however, sparked a major controversy,[17,18] which appears to have introduced sufficient doubt about the efficacy of sulfinpyrazone that its use has essentially been abandoned. The change is all the more remarkable given the increased acceptance of the platelet active agents aspirin and dipyridamole in the postinfarction setting.

This study, like all surveys, has certain inherent limitations. First, the data represent what physicians say they do in practice, rather than being an actual audit of their practices. Second, many physicians did not respond to the survey. Since relatively more cardiologists responded than internists or family and general practitioners, our results are reported according to specialty. Clearly, the nonrespondents may differ from the respondents in other ways, and caution must be used in extrapolating these results to all physicians. However, since the analysis of time trends is referenced to previous surveys, which share these same limitations, we believe the trends reported here reflect true shifts in practice patterns.

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Influence of Long-Term Metoprolol Treatment on Early and Late Exercise Test Performance After Acute Myocardial Infarction

GUNNAR OLSSON, MD, PhD, NINA REHNQVIST, MD, PhD,
ULLA FREYSCHUSS, MD, PhD, and STAFFAN ZETTERQUIST, MD, PhD

The effect of therapy on exercise performance during a 3-year follow-up after acute myocardial infarction (AMI) was evaluated in a double-blind randomized comparison between 154 patients given metoprolol (100 mg twice daily) and 147 patients given placebo. Exercise tests were performed 1.5, 6, 12, 24 and 36 months after AMI. Maximal accomplished workloads were similar in the 2 groups throughout follow-up. Maximal heart rate was significantly higher in the placebo-treated group throughout the study ($p < 0.001$). At the 6-week test more patients in the placebo group terminated exercise due to angina pectoris (40 vs 25%, $p < 0.05$) and showed exercise-induced ST-depressions (38 vs 27%, $p = 0.05$) compared with the metoprolol group. Exercise-induced ventricular arrhythmias were significantly more common in the placebo group during the initial 6 months. Death, another AMI or both were significantly reduced by metoprolol treatment in patients with exercise-induced ST depression ≥ 1 mm at the 6-week test. In a multiple logistic regression analysis maximal accomplished workload at 6 weeks ($p < 0.026$), male sex (relative risk [rr] = 3.57, $p = 0.016$), previous AMI (rr = 3.07, $p = 0.001$), therapy with placebo (rr = 2.14, $p = 0.007$) and left ventricular failure (rr = 2.04, $p = 0.023$) were shown to carry independent prognostic information as well as exercise-induced ST-depression (≥ 1 mm) in placebo-treated patients (rr = 2.70, $p = 0.01$).

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In recent years post-acute myocardial infarction (AMI) trials have convincingly shown that treatment with certain β blockers improves prognosis.[1] It is, however, important to investigate other potential effects of treatment, such as symptoms and physical fitness. The present study investigates certain aspects of post-AMI treatment with metoprolol. The effects of the treatment on ventricular arrhythmias and prognosis have previously been published.[2–4] In this report we describe the effect of post-AMI metoprolol treatment on performance on repeated exercise tests during a 3-year follow-up. The prognostic value of an exercise test performed 6 weeks after AMI was also evaluated and the possible influence of metoprolol treatment was analyzed.

From the Department of Medicine, Karolinska Institute, and the Department of Clinical Physiology, Danderyd Hospital, Danderyd, and the Department of Clinical Physiology, Huddinge Hospital, Huddinge, Sweden. This study was supported by grants from Karolinska Institute, The Swedish National Association against Chest and Heart Diseases, and AB Hässle, Mölndal, Sweden. Manuscript received February 17, 1987; revised manuscript received October 23, 1987, and accepted October 25.

Address for reprints: Gunnar Olsson, MD, Department of Medicine, Karolinska Institute, Danderyd Hospital, S-182 88 Danderyd, Sweden.

Methods

The Stockholm Metoprolol Trial was a prospective, double-blind, placebo-controlled study of patients after AMI. A detailed description of the study has been reported previously.[3] In brief, 301 survivors of AMI younger than 70 years of age, in sinus rhythm and without bundle branch block or contraindications for β blockade were stratified prospectively according to ventricular arrhythmias on a long-term electrocardiographic registration, infarct size as estimated by enzyme maximum and age. Thereafter the patients were randomized to 3 years of double-blind treatment with metoprolol 100 mg twice daily (n = 154) or placebo (n = 147). Treatment started 7 to 14 days after the acute event. No patient was lost during the follow-up as regards information on mortality and morbidity. Patients were included between May 1976 and December 1980.

TABLE I Baseline Characteristics

Variables	Placebo (n = 147)	Metoprolol (n = 154)
Mean age (yrs)	59 ± 7	60 ± 7
Men (%)	83	78
Previous AMI (%)	20	21
History of SH (%)	28	23
Cerebrovascular event before AMI (%)	3	5
Q-wave AMI (%)	72	75
Site of AMI		
Anterior (%)	51	44
Inferior (%)	31	38
Unknown (%)	18	18
LDH_t (ukat/liter)	19.6 ± 13.7	19.8 ± 14.0
VF in CCU (%)	3	3
Rales in CCU (%)	67	65
SBP <90 mm Hg in CCU (%)	10	10
Complex VPCs at randomization (%)	33	38
Treatment at discharge		
Digitalis (%)	24	23
Diuretics (%)	48	42
Antiarrhythmics (%)	6	6

AMI = acute myocardial infarction; CCU = coronary care unit; LDH_t = peak value of the thermostable fraction of lactate dehydrogenase; SBP = systolic blood pressure; SH = systemic hypertension; VF = ventricular fibrillation; VPCs = ventricular premature complexes.

Patients were withdrawn from study treatment if there was an obvious need for β blockade or if suspected severe side effects developed.[3] All surviving patients were followed for the entire 3 years. Exercise tests were performed 6 weeks and 6, 12, 24 and 36 months after the AMI with bicycle ergometer (Siemens-Elema). The workload started with 20 watts and increased by 10 watts/min[5] until limiting symptoms, hemodynamically important ventricular arrhythmias or severe ST depression (>4 mm) appeared. The following parameters from the exercise tests were used in the analysis: maximal workload, exercise limiting factor (angina pectoris, dyspnea, serious arrhythmia, severe ST depression, fatigue), maximal heart rate, exercise-induced ST depression ≥1 mm (0.1 mV) 0.06 second after the J point and ventricular arrhythmia during the test.

All patients gave their informed consent for participation in the study, which was approved by the local ethical committee.

Statistical analysis: In the statistical analyses the Student *t* test was used to compare continuous variables. In text data are presented as mean ± standard deviation. For comparisons of categorical variables the chi-square test was used. To evaluate the prognostic value of the 6-week exercise test a multiple logistic regression analysis was performed. In this analysis baseline characteristics as well as parameters obtained from the 6-week exercise test were included and tested for (1) death and (2) another AMI, death or both. All statistical analyses were performed in 2-tailed fashions. A p value <0.05 was considered significant. All statistical analyses have been performed according to initial drug allocation ("intention to treat"), unless otherwise stated.

Results

The 2 treatment groups were well balanced with no significant differences in pretreatment variables (Table I). Detailed mortality and morbidity data have been reported elsewhere,[3] but for clarity we will give a brief summary. There were 31 deaths (29 cardiac) in the placebo group compared with 25 (20 cardiac) in the metoprolol group (difference not significant). Thirty-one placebo-treated patients had another nonfatal AMI, compared with 18 in the metoprolol group (p <0.05). During the 3 years, 35 and 38 patients in the placebo and metoprolol groups, respectively, were withdrawn from study treatment.[3]

At the 6-week test calcium antagonists were given to 17 placebo patients (7 verapamil, 6 nifedipine, 4 prenylamine) and to 4 (p <0.05) metoprolol patients (1 nifedipine, 3 prenylamine). Corresponding numbers for long-acting nitrates were 32 and 17 (p <0.05).

Exercise tests: In 25 patients the initial 6-week exercise test is missing (8 placebo and 17 metoprolol). The reasons for missing tests in the placebo group are:

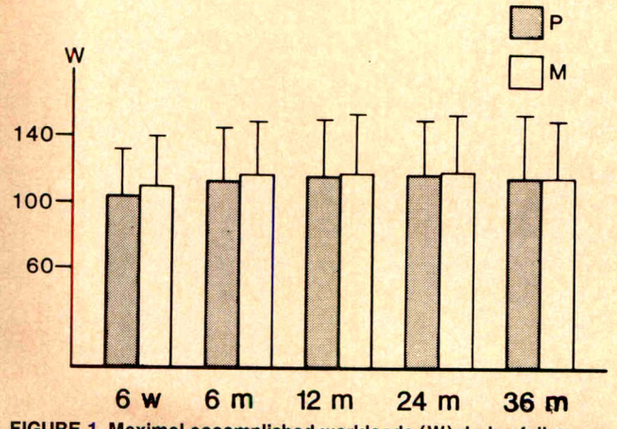

FIGURE 1. Maximal accomplished workloads (W) during follow-up. M = metoprolol; m = months; P = placebo; w = weeks. Number of patients as in Table II.

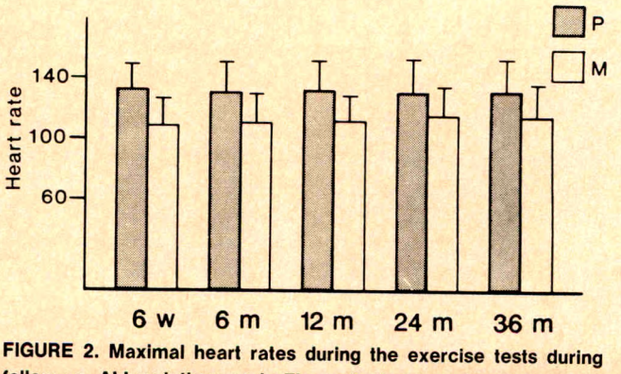

FIGURE 2. Maximal heart rates during the exercise tests during follow-up. Abbreviations as in Figure 1. Number of patients as in Table II. The differences between the 2 groups were significant (p <0.001).

TABLE II Reasons for Termination of Exercise Tests

	Placebo						Metoprolol					
	No.	Angina	Dyspnea	Arrhythmia	ST↓	Fatigue	No.	Angina	Dyspnea	Arrhythmia	ST↓	Fatigue
6 weeks (%)	139 (88)	40 (33)	19 (18)	2 (2)	4 (7)	35 (40)	137 (92)	25* (24)	25 (23)	2 (3)	3 (3)	45 (47)
6 months (%)	133 (88)	25 (23)	26 (27)	2 (2)	3 (3)	44 (45)	140 (92)	24 (18)	21 (21)	1 (1)	3 (3)	51 (57)
12 months (%)	127 (86)	30 (27)	24 (27)	2 (0)	2 (2)	42 (44)	137 (93)	23 (23)	18 (16)	1 (0)	3 (3)	55* (58)
24 months (%)	112 (83)	27 (25)	20 (23)	2 (2)	3 (1)	48 (49)	129 (90)	21 (16)	27 (27)	1 (1)	2 (2)	49 (54)
36 months (%)	105 (83)	33 (32)	23 (24)	2 (2)	1 (1)	41 (41)	122 (92)	21 (17)*	30 (31)	1 (1)	0 (0)	48 (51)

Values derived according to "intention to treat"/"on drug 36 months."
* $p < 0.05$ compared with placebo group.
ST↓ = ST-segment depression.

4 deaths, 2 due to arrhythmia, 1 unwillingness, 1 unknown cause. In the metoprolol group the following reasons for missing tests are: 6 deaths, 2 re-AMI, 3 unwillingness and 6 unknown causes. Two and 4 patients in the placebo and metoprolol groups, respectively, with missing tests subsequently died.

Maximal workloads at the 6-week test were 104 ± 29 and 110 ± 32 watts in the placebo and metoprolol groups, respectively (difference not significant). Maximal workload increased significantly to maximum values of 117 ± 34 and 119 ± 37 in the 2 groups, respectively, at 24 months. Maximal accomplished workloads in the 2 groups are shown in Figure 1.

Maximal heart rate at the 6-week exercise test was 133 ± 17 beats/min in the placebo group and 109 ± 19 beats/min in the metoprolol group ($p < 0.001$). During the follow-up maximal heart rate was always lower in the metoprolol group compared with the placebo group ($p < 0.001$, Figure 2).

Reasons for termination of exercise tests are shown in Table II. In the placebo group there was a significantly larger proportion of patients terminating due to angina at the 6-week test than in the metoprolol group (40 vs 25%, $p < 0.05$). At 12 months a significantly larger proportion of patients terminated exercise due to fatigue in the metoprolol group than in the placebo group (55 vs 42%, $p < 0.05$). When analyzing patients who actually continued to receive study treatment ("on drug 36 months"), more patients in the placebo group experienced angina pectoris during exercise at 36 months (32 vs 17%, $p < 0.05$).

In the placebo group 38% of the patients showed ≥1 mm ST-depression during the 6-week test. The corresponding figure in the metoprolol group is 27% ($p = 0.05$). The rate of mortality, another AMI or both among patients with ST depression ≥1 mm was 45% in the placebo group and 22% in the metoprolol group ($p < 0.05$). Corresponding figures for patients without ST depressions are 15 and 9%, respectively (difference not significant).

During the exercise test at 6 weeks 48% of the placebo patients showed any type of ventricular arrhythmia compared with 28% of the metoprolol patients ($p < 0.001$). The corresponding figures at the 6-months test were 45% and 31% ($p < 0.05$). The proportions of patients with ventricular arrhythmia during exercise are shown in Figure 3.

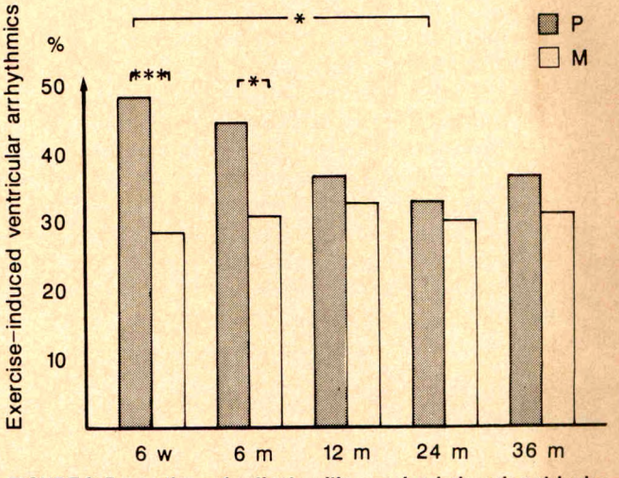

FIGURE 3. Proportions of patients with exercise-induced ventricular arrhythmias during follow-up. Abbreviations as in Figure 1. Number of patients as in Table II. * $p < 0.05$; *** $p < 0.001$.

Prognostic implications from the six-week exercise test: In the multiple logistic regression analysis the following variables were entered: treatment group, sex, smoking habits, previous AMI, type of index AMI, signs of left ventricular failure in the coronary care unit, digitalis and diuretic treatment at discharge, complex ventricular arrhythmias at a predischarge 6-hour electrocardiographic recording, age and LD_t-maximum (peak value of thermostable fraction of lactate-dehydrogenase). From the 6-week exercise test, ventricular arrhythmia, exercise-limiting factor, ≥1 mm ST depression and maximal workload were used.

When death was set to be the dependent variable, previous AMI (relative risk [rr] 3.07, $p = 0.001$), maximal workload ($p = 0.026$) and male sex (rr 3.57, $p = 0.016$) were found to carry significant prognostic information for the following 3 years for the entire data base (i.e., the 2 treatment groups taken together). In this model the value for "goodness of fit" was 0.829. For the prediction of death, another AMI or both, the following variables carried significant prognostic weight: previous AMI (rr 2.76, $p = 0.002$), placebo treatment (rr 2.14, $p = 0.007$), heart failure in the coronary care unit (rr 2.04, $p = 0.023$) and male sex (rr 2.32, $p = 0.044$). The "goodness of fit" was 0.957.

In a second step, the multiple logistic regression analysis was applied to the 2 separate treatment groups to derive information on treatment influence on risk indicators. In this analysis ST depression ≥1 mm was shown to be an independent risk indicator for death, another AMI or both in the placebo group (rr 2.7, p = 0.01). In the metoprolol group, however, ST depression was not associated with worsened prognosis.

Any major cardiac event among patients with angina at the 6-week exercise test was significantly more common in the placebo group (23 of 55, 42%) than in the metoprolol group (5 of 34, 15%) (p <0.01). In the placebo group these events consisted of another AMI in 10 patients (2 subsequently died), deaths in 9 and coronary artery bypass grafting in 4. Corresponding figures in the metoprolol group were 1, 2 and 2. In patients who did not experience angina during the initial exercise test, any major cardiac event occurred in 29 (35%) and 19 (19%) patients in the placebo and metoprolol groups (p <0.05), respectively. These events consisted of another AMI in 18 patients (6 subsequently died), deaths in 8 and 3 underwent coronary artery bypass grafting. Corresponding figures in the metoprolol group were another AMI in 9 patients (4 subsequently died), deaths in 9 and coronary artery bypass grafting in 1. In a separate univariate analysis in patients without previous AMI, mortality was significantly reduced in the metoprolol patients (3.2 vs 7.7% in placebo, p <0.05).

Discussion

In the present study metoprolol treatment after AMI did not influence maximal workload. Similarly, timolol treatment after AMI has also been shown not to influence the working capacity.[6] Probably, these findings are partly explained by the large proportion of patients receiving both β blockers and placebo who terminate exercise because of reasons other than angina. Further, the more frequent use of other antianginal drugs in the placebo group may well have influenced the results. Despite this more frequent use of other antianginal drugs, angina during the 6-week exercise test was more common in the placebo than in the metoprolol group. At 6 months, however, no significant difference in exercise limiting factors was found between the groups. Interestingly, maximal workload was similar in the 2 treatment groups, although reasons for termination sometimes differed (e.g., at 6 weeks angina was more common in the placebo group, at 12 months fatigue was more common in the metoprolol group).

Exercise-induced ventricular arrhythmias were more common in the placebo group during early follow-up. These findings are in agreement with previous reports.[7,8] The clinical significance of this finding is not clear. When ventricular arrhythmias were recorded by repeated Holter monitorings,[2] we noted another pattern. Continuous increases in both complexity and frequency of ventricular arrhythmias by time in the placebo group occurred. These increases were counteracted by metoprolol treatment. However, in that evaluation an early decrease in premature ventricular complexes was indeed seen by metoprolol therapy, indicating also an acute antiarrhythmic action.

In patients who actually continued to receive study treatment throughout the 3 years, the proportions of patients with angina as limiting symptom initially after the AMI were similar in the 2 groups. At 3 years, however, significantly more patients in the placebo group terminated exercise due to angina. These results—in combination with the improved prognosis in patients treated with metoprolol and the effect on chronic ventricular arrhythmias[2]—may indicate that the course of the disease is positively influenced by β-adrenoceptor blockade. Whether this reflects influence on the underlying disease or only the manifestations of the disease is yet unclear.

In several previous studies the prognostic information of an exercise test after AMI has been evaluated. Thus, the prognostic importance of ischemia-induced electrocardiographic abnormalities,[9–18] exercise-induced ventricular arrhythmias,[12,19–22] abnormal blood pressure response[22,23] and functional capacity[9,22,24–27] has been shown. In the present study maximal workload carried independent prognostic value in the entire material. In the placebo group exercise-induced ST depression ≥1 mm also carried significant prognostic information. Interestingly, this was not found in the metoprolol group, similar to results from Krone et al.[18] Other clinical factors with independent prognostic weight were sex, previous infarction, therapy without β blockers and left ventricular impairment.

Metoprolol treatment in patients with signs of ischemia (angina or ST depressions) was beneficial. However, active treatment also improved prognosis in so-called low-risk patients, that is, those without angina pectoris or previous infarction.

In conclusion, treatment with metoprolol after AMI does not influence maximal exercise capacity. Exercise-induced angina and ST depression early after AMI are reduced by metoprolol. Maximal workload at 6 weeks, male sex, previous infarction, therapy without β blockers and left ventricular heart failure carry prognostic information. Exercise-induced ST depression in patients who are not treated with β blockers also has prognostic value, but not in those treated with β blockers.

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Improved Survival up to Four Years After Early Coronary Thrombolysis

DETLEF G. MATHEY, MD, JOACHIM SCHOFER, MD, FLORENCE H. SHEEHAN, MD, HANS-JOACHIM KREBBER, MD, MARLENE JUSTEN, MD, GEORG RODEWALD, MD, H.T. DODGE, MD, and WALTER BLEIFELD, MD

The long-term prognosis after thrombolytic therapy in patients with acute myocardial infarction (AMI) is unknown. This question was investigated in a 4-year follow-up study of 227 patients. According to the status of reperfusion at the end of the acute catheterization, the patients were divided into a patent (n = 171) and an occluded (n = 56) group. Both hospital and 4-year mortality rates were significantly reduced in the patent group by 13 and 14%, respectively ($p \leq 0.005$ for both). Baseline variables known to be important for prognosis did not differ between the 2 groups. Patients with a patent infarct artery who underwent early acute coronary artery bypass grafting (CABG) had a greater survival ($p < 0.10$) and better left ventricular function ($p < 0.01$) than did patients with a patent infarct artery who did not undergo CABG. This difference was associated with a lower frequency of fatal reinfarction and cardiogenic shock in the CABG group. Thus, survival is improved up to 4 years after successful thrombolysis and appears to be further enhanced by early CABG.

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Several years after its introduction,[1–3] intracoronary and intravenous thrombolytic therapy clearly shows a positive effect on hospital mortality[4,5] in acute myocardial infarction (AMI). In addition, 1-year follow-up results have been reported from 2 trials.[6,7] Whereas the initial reduction in hospital mortality was fully maintained in the Dutch trial,[7] it was partly lost in the Western Washington trial[6] by 1 year. In both trials, a substantial proportion of patients underwent revascularization by either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG). Long-term prognosis beyond 1 year, however, is unknown. This study observed patients up to 4 years after thrombolytic therapy and analyzed the factors contributing to their survival.

Methods

Patient population: Patients with AMI were enrolled in the study, if they were admitted within 3 hours of the onset of chest pain and had ≥2 mm ST-segment elevation on the electrocardiogram. They underwent immediate (onset of treatment ≤5 hours after symptom onset) thrombolytic therapy with intracoronary streptokinase between 1979 and 1983 (n = 174) or intravenous urokinase during 1983 and 1984 (n = 56).[8,9] Patients receiving intravenous urokinase were studied within 1 hour after initiation of therapy. PTCA was performed in 19 patients with severe residual stenosis after thrombolytic therapy. Reperfusion was achieved by PTCA in 17 of 25 patients whose infarct artery remained occluded after thrombolytic therapy.

Clinical follow-up: Between April 1985 and April 1987, patients were contacted to determine vital status, and the date of death or rehospitalization, if applicable. Reinfarction was defined as an infarct that occurred in the same location as when the patient was enrolled in the study and was diagnosed on the basis of typical electrocardiographic and enzyme changes. The cause of death and the reason for rehospitalization were determined from the patient's medical record. Data on vital status could be obtained in 227 (99%) of the 230 consecutively enrolled patients.

From the Departments of Cardiology and Cardiovascular Surgery, University Hospital Eppendorf, Hamburg, West Germany, and the Cardiovascular Research and Training Center, University of Washington, Seattle, Washington. This study was supported in part by the Dr. Werner-Otto-Stiftung, Hamburg, West Germany, a grant from the R.J. Reynolds Foundation, Winston-Salem, North Carolina, and grant HL 19451 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received August 14, 1987; revised manuscript received October 23, 1987, and accepted October 25.

Address for reprints: Detlef G. Mathey, MD, Department of Cardiology, University Hospital Eppendorf, Martinistrasse 52, 2000 Hamburg 20, West Germany.

TABLE I Characteristics of Patients Who Survived or Died After Thrombolytic Therapy

	Survived	Died	p Value*
Pts (n)	186	41	
Mean age (yrs)	54 ± 12	63 ± 11	0.001
Men (%)	87	63	0.001
History of systemic hypertension (%)	31 (147)	63 (32)	0.001
Diabetes mellitus (%)	8 (153)	20 (30)	NS
Hyperlipidemia (%)	35 (144)	17 (29)	0.065
Previous AMI (%)	14 (150)	30 (33)	0.024
Infarct location (% anterior)	59 (182)†	58 (38)	NS
Coronary disease (% 1-vessel)	36 (173)	30 (37)	NS
Q wave on admission ECG (%)	32 (139)	34 (32)	NS
Maximum ST-segment elevation (mm)	4.5 ± 4.0 (135)	3.6 ± 2.0 (33)	0.078
Arrhythmias in CCU (% none/VT/VF)	68/18/14 (126)	54/7/39 (28)	0.007
LV ejection fraction (%)	55 ± 12 (133)	44 ± 16 (16)	0.001
Hypokinesis in infarct site (SD)	−2.4 ± 1.1 (133)	−2.7 ± 1.0 (16)	NS
Hyperkinesis in noninfarct site (SD)	0.7 ± 1.5 (133)	0.0 ± 1.4 (16)	0.071
Patency of the infarct artery at end of acute catheterization (%)	79	59	0.006
Early bypass surgery (%)	33	17	0.047
Percutaneous transluminal coronary angioplasty (%)	28 (120)	32 (31)	NS

* Chi square for dichotomous variables, unpaired *t* test for continuous variables, differences are significant if $p < 0.05$, but p values > 0.05 and < 0.10 are included for interest.

† Parentheses indicate number of patients if data are incomplete.

CCU = coronary care unit; ECG = electrocardiogram; LV = left ventricular; MI = myocardial infarction; NS = difference not significant; SD = standard deviation from normal; VF = ventricular fibrillation; VT = ventricular tachycardia.

CABG was defined as early if performed within 14 days after AMI. The indications for early CABG were: (1) a patent infarct artery with a residual stenosis >70% in conjunction with recurrent ischemic events, scintigraphic evidence of myocardial salvage, or both and (2) severe lesions in other vessels limiting prognosis (left main disease or left main equivalent).

In patients undergoing CABG <24 hours after thrombolysis, care was taken to prime the heart lung machine with 2 to 3 units of whole blood to improve the coagulation status. Two patients received supplemental infusions of fibrinogen.[10]

Angiographic analysis: The severity and the extent of coronary artery disease and the patency of the infarct artery were assessed visually by the consensus of 2 observers. Patency immediately after thrombolysis was defined as complete opacification of the infarct artery with normal rates of filling and clearing of contrast. Patients with only partial reperfusion, that is, incomplete artery opacification, or slow filling or clearing of contrast, were not considered to be successfully reperfused.

Left ventricular (LV) function was analyzed at the University of Washington from the cine films. LV volume was calculated by the area-length method. Wall motion abnormality in the infarct and noninfarct regions was calculated by the centerline method and expressed in standard deviations per chord as previously described.[11]

Scintigraphic studies: In 69 patients, who were admitted when the isotope and nuclear medicine personnel were available, intracoronary myocardial scintigraphy with thallium-201 was performed in the catheterization laboratory using a mobile gamma camera before and immediately after thrombolysis.[12] Scintigraphic evidence of myocardial salvage was defined as significant new thallium uptake with no or only a small residual thallium defect as judged by 2 independent observers.

Statistical analysis: Comparisons between patient groups were performed using the unpaired *t* test for continuous variables and chi-square for dichotomized variables. The change in LV function between acute and follow-up study was assessed using paired *t* test. Differences in long-term survival were assessed using life table analysis. The contribution of factors to survival was evaluated using *t* test for continuous variables, and chi-square or Fisher's exact test for dichotomous variables. Statistical significance was defined as $p < 0.05$; however, p values > 0.05 and < 0.10 are included for interest.

Results

Identification of factors influencing survival: Table I lists clinical variables evaluated for their correlation with vital status. Patients who died differed significantly from those who survived in age, sex, arrhythmia in the cardiac care unit, history of angina, systemic hypertension, previous AMI, infarct artery patency and whether or not CABG was performed early. Although data were not complete for these parameters, bias is unlikely because the occurrence of missing data was similar for survivors and nonsurvivors. LV function measured acutely was also significantly more depressed in patients who died; for this parameter the actual differences may be greater because ventriculography was omitted in the majority of patients who subsequently died.

TABLE II Characteristics of Patients With and Without a Patent Infarct Artery

	Patent	Not Patent	p Value
Pts (n)	171	56	
Mean age (yrs)	55 ± 12	58 ± 11	NS
Men (%)	84	77	0.090
Infarct location, % anterior	58	62	NS
Coronary disease, % 1-vessel	36	32	NS
Q wave on admission ECG (%)	33 (130)	29 (42)	NS
Maximum ST-segment elevation (mm)	4.4 ± 3.9 (127)	4.0 ± 3.0 (41)	NS
Arrhythmias in CCU (% none/VT/VF)	68/17/15 (119)	54/14/32 (35)	0.095
LV ejection fraction (%)	53 ± 13 (125)	52 ± 13 (26)	NS
Hypokinesis in infarct site (SD)	−2.5 ± 1.0 (125)	−2.5 ± 1.6 (26)	NS
Hyperkinesis in noninfarct site (SD)	0.7 ± 1.5 (125)	0.5 ± 1.5 (26)	NS
Percutaneous transluminal coronary angioplasty (%)	30 (115)	25 (36)	NS

Abbreviations as in Table I.

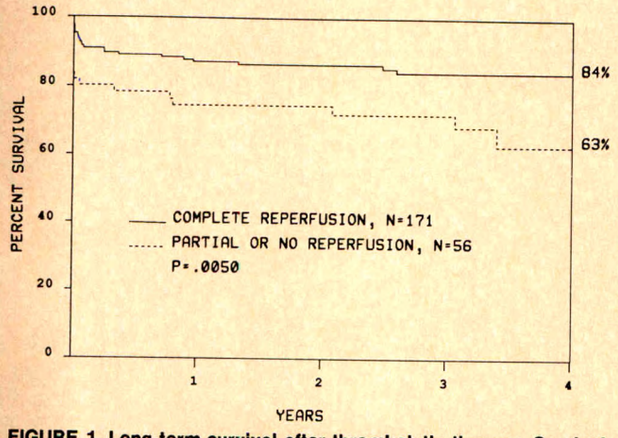

FIGURE 1. Long-term survival after thrombolytic therapy. Survival was significantly ($p \leq 0.005$) greater in patients who had a patent infarct artery at the end of the acute cardiac catheterization than in patients with partial or no reperfusion.

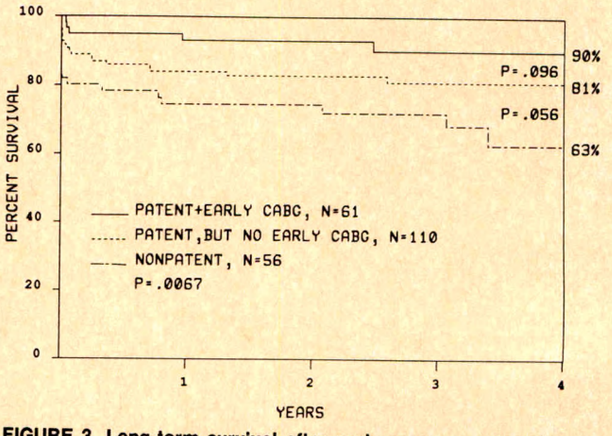

FIGURE 3. Long-term survival after early coronary artery bypass surgery (CABG). Patients who underwent surgery within 14 days after infarction had better survival than those without reperfusion or those with a patent infarct artery but who did not undergo CABG.

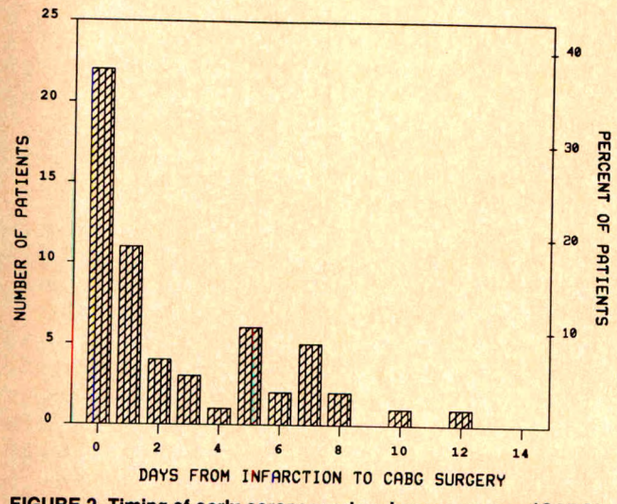

FIGURE 2. Timing of early coronary artery bypass surgery (CABG). Most patients were operated on within the first 2 days after infarction.

Coronary artery patency: Survival was significantly better ($p < 0.005$) in patients who achieved a patent infarct artery at the end of the acute cardiac catheterization than in those with an occluded artery (Figure 1). This difference was apparent at 10 days and was maintained up to 4 years after AMI. The baseline characteristics of these 2 groups did not differ before thrombolysis (Table II). After thrombolysis, early CABG was performed more frequently in patients with a patent infarct artery (Table III).

Early coronary artery bypass grafting in patients with patent infarct arteries: Early CABG was usually performed in the first 2 days after AMI (Figure 2). On the average, 2.6 grafts per patient were implanted, 92% of which were angiographically patent at follow-up approximately 1 month later. Despite abnormal coagulation values at the beginning of surgery in most patients, the intra- and postoperative blood loss was not greater in patients operated on the day of thrombolysis than in those operated later.[13] Hospital mortality in the operated patients was 3.2%.

TABLE III Follow-Up Characteristics of Patients With and Without a Patent Infarct Artery

	Patent	Not Patent	p Value
Peak creatine kinase (mg/dl) (%)	1,106 ± 994 (144)	1,379 ± 948 (44)	NS
LV ejection fraction (%)	53 ± 13 (110)	48 ± 10 (24)	NS
Hypokinesis in infarct site (SD)	−1.9 ± 1.2* (110)	−2.3 ± 1.2 (24)	NS
Hyperkinesis in noninfarct site (SD)	0.3 ± 1.3* (110)	−0.3 ± 1.3 (24)	0.055
Early CABG (%)	36 (171)	11 (56)	0.001

* $p < 0.001$ versus acute, paired *t* test in 90 patients.
Abbreviations as in Table I.

TABLE IV Baseline Characteristics in Patients with a Patent Infarct Artery With or Without Early Coronary Artery Bypass Graft (CABG) Surgery

	CABG	No CABG	p Value
Pts (n)	61	110	
Mean age (yrs)	52 ± 11	56 ± 13	0.054
Men (%)	87	83	NS
History of previous AMI (%)	28 (50)	13 (89)	0.035
Systemic hypertension (%)	34 (47)	43 (91)	NS
Diabetes mellitus (%)	13 (93)	6 (48)	NS
Hyperlipidemia (%)	43 (46)	30 (88)	NS
Infarct location (% anterior)	40 (60)	44 (107)	NS
Coronary disease (% 1-vessel)	33 (57)	37 (103)	NS
Q wave on admission ECG (%)	33 (42)	33 (87)	NS
Maximum ST-segment elevation (mm)	4.2 ± 2.9 (39)	4.5 ± 4.3 (88)	NS
Arrhythmias in CCU (% none/VT/VF)	68/19/13 (37)	68/16/16 (82)	NS
LV ejection fraction (%)	56 ± 11 (48)	52 ± 12 (76)	0.06
Hypokinesis in infarct site (SD)	−2.3 ± 1.1 (48)	−2.6 ± 1.0 (76)	NS
Hyperkinesis in noninfarct site (SD)	0.8 ± 1.5 (48)	0.6 ± 1.4 (76)	NS
Change in thallium scintigram after thrombolysis, % improved/unchanged/worse	70/20/10 (20)	9/50/41 (22)	0.001
Thallium perfusion defect size after thrombolysis, % no defect/small/large	5/0/95 (20)	4/14/82 (22)	NS

Abbreviations as in Table I.

Patients with a patent infarct artery who underwent early CABG had a 90% 4-year survival rate; there was an 81% survival rate in the patent nonoperated group (Figure 3) ($p = 0.096$). The poorest survival (63%) was seen in patients with occluded infarct arteries ($p < 0.06$ vs nonoperated).

Because it was used as a criterion for early CABG, perfusion on thallium scintigraphy was more frequently improved in patent, operated than in nonoperated patients. However, the residual perfusion defect after thrombolysis was large in both groups. There was no significant difference between the operated and nonoperated groups in any of the other baseline characteristics tested, nor were there significant intergroup differences in the incidence of missing data (Table IV). However, LV function at follow-up was significantly better in the operated patients (Figure 4). Wall motion in the infarct region improved only in the operated patients. Motion in the noninfarct region remained hyperkinetic in operated patients instead of decreasing to normal levels by follow-up, as it did in the nonoperated group. This resulted in a higher follow-up ejection fraction in the operated patients of 57 ± 12 ($n = 36$) versus 50 ± 12% ($n = 73$) in nonoperated patients ($p < 0.01$).

Causes of death: Forty-two patients died. Of those who died of cardiogenic shock only 1 was in the operated group compared with 4 in the patent, nonoperated group and 7 in the occluded group. Death by reinfarction occurred in 6 patients in the patent, nonoperated group but only 1 in the operated group.

Rehospitalization: The rate of rehospitalization (Figure 5) for cardiac indications, such as angina, congestive heart failure, arrhythmias or reinfarction, was only 13% over the 4-year period, and was similar in the operated, patent nonoperated and occluded groups.

Discussion

This study is the first to observe and report long-term survival after thrombolysis. The data indicate that survival is significantly better up to 4 years after AMI in patients in whom a patent infarct artery is achieved compared with patients in whom the infarct artery remains occluded. Patients who undergo early CABG after successful thrombolysis because of a high-grade residual stenosis in conjunction with scintigraphic evidence of myocardial salvage, recurrent ischemic events or severe, multivessel disease have a

higher survival rate than patients with successful thrombolysis but who do not undergo CABG.

The difference in survival between our patients with complete reperfusion compared with those with persistent occlusion or partial reperfusion agrees with data from the Western Washington trial[6] showing significantly greater survival after complete reperfusion than after partial or no reperfusion. Could factors other than infarct artery patency explain this difference in survival? Baseline characteristics known to be important for prognosis did not differ significantly between the patent and the occluded group. Thus, the 2 groups were comparable before thrombolysis. After thrombolysis, a reduction in infarct size in the patent group may have been responsible for their better prognosis, because they had better LV function and slightly lower peak creatine kinase levels. That successful thrombolytic therapy may also benefit function in the noninfarct region has been observed in other trials.[14,15] The lack of a significant difference in LV function is probably due to the frequent omission of ventriculography in patients who had an occluded artery. The most significant difference between the 2 groups was the higher incidence of early CABG in the patent group.

When the patient with a patent infarct artery were further subdivided according to whether they underwent early CABG, the CABG group was found to have better survival. Because the patients were not randomly assigned to early CABG but were selected according to the indications mentioned, it is difficult to give a definite explanation for this observation from our study. Some aspects, however, can help to clarify the problem. First, the baseline characteristics did not differ significantly between the operated and patent but nonoperated groups, although operated patients tended to be younger. Instead, there was greater risk in the operated group due to the significantly higher incidence of previous AMI. Second, performance of early CABG was not associated with undue morbidity and mortality.[13] Thus, since baseline characteristics and complications of surgery cannot explain the survival difference, this difference is most likely due to the effect of therapy. The enhanced survival in the operated group may be due to myocardial salvage resulting from better perfusion or the protective effect of early CABG or both. As evidence for myocardial salvage,

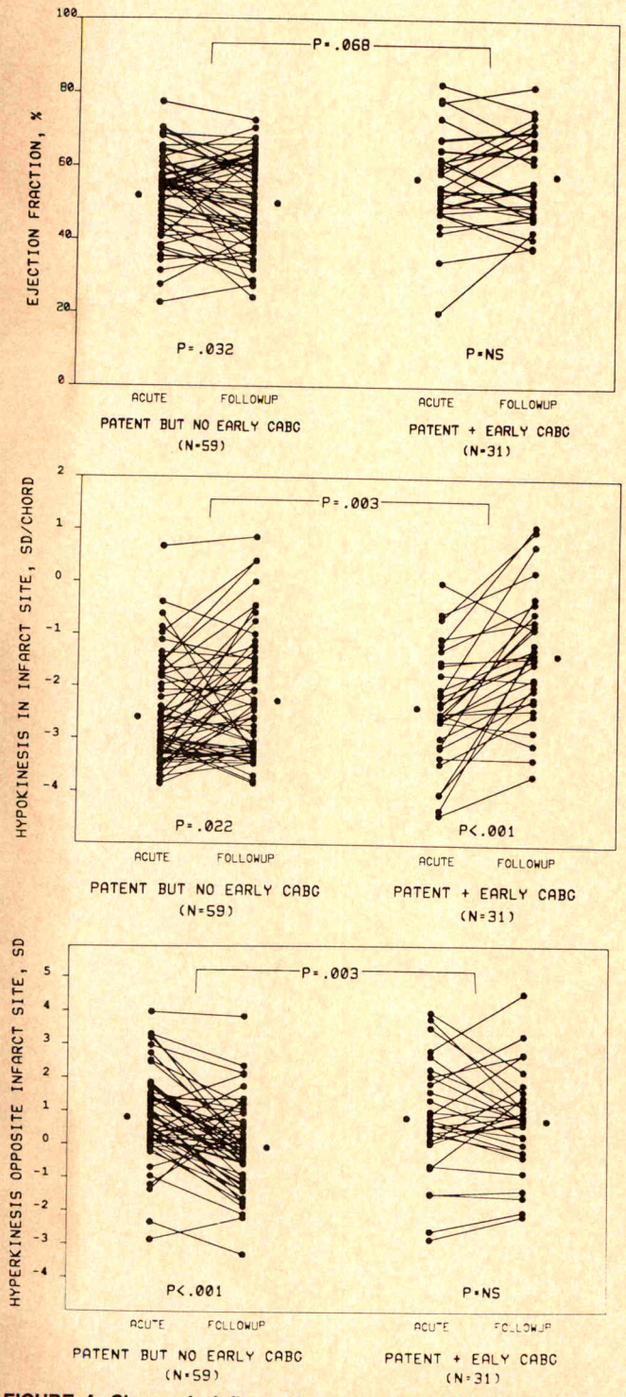

FIGURE 4. Change in left ventricular function after thrombolytic therapy ± coronary artery bypass surgery (CABG). The influence of hypokinesis in the infarct region and hyperkinesis in the noninfarct region on the global ejection fraction can be seen.

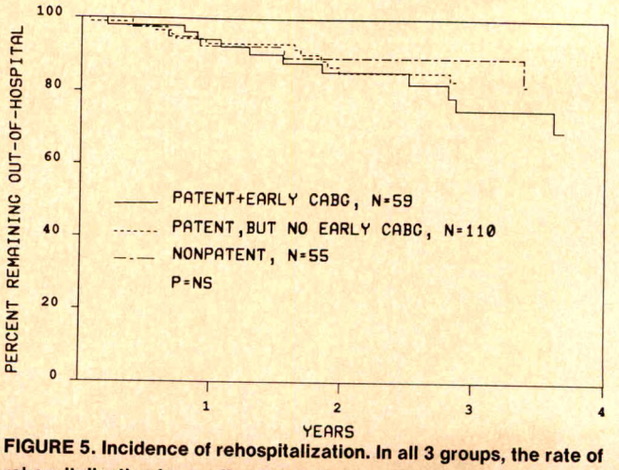

FIGURE 5. Incidence of rehospitalization. In all 3 groups, the rate of rehospitalization for cardiac indications was similarly low. CABG = coronary artery bypass grafting.

LV function at follow-up was significantly greater in the operated group. Because effective thrombolytic therapy exposes the patient to an increased risk of recurrent AMI,[7] the lower incidence of death by reinfarction among our operated patients suggests that early CABG enhanced survival by maintaining the beneficial effect of thrombolysis.

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Factors of Importance for Prognosis in Men with Angina Pectoris Derived from a Random Population Sample

The Multifactor Primary Prevention Trial, Gothenburg, Sweden

MARIANNE HAGMAN, MD, LARS WILHELMSEN, MD, KJELL PENNERT, BSc, and HANS WEDEL, PhD

A random population sample of middle-aged men from the Primary Prevention Trial was followed for 11.3 years from a first screening when different factors known to be associated with coronary artery disease (CAD) were analyzed. Men with uncomplicated angina pectoris (AP) (n = 167) derived from this population had an incidence of fatal and nonfatal CAD events 3 times higher than that of men without AP or myocardial infarction (n = 5,774). Men with myocardial infarction with or without AP had an incidence of CAD events 7 to 8 times higher than that of men without AP or myocardial infarction. Similar differences were found for new cases of uncomplicated AP (n = 128) and myocardial infarction detected at a second screening after 4 years and followed for 7.3 years. Pooled data from this series of men with uncomplicated AP showed the following factors to be associated in multivariate analysis with nonfatal or fatal CAD endpoints during follow-up: elevated serum cholesterol, elevated blood pressure, smoking and attack score. The risk increase associated with the first 3 factors was similar to the general population. These findings indicate that the same factors affecting prognosis after a first appearance of AP affect similarly patients with myocardial infarction and clinically healthy subjects. Preventive measures against these risk factors seem to be of similar importance among patients with AP, post-infarct patients and healthy subjects.

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The natural history of angina pectoris (AP) was first studied approximately 70 years ago, with 1 of the most extensive series of AP cases from that time described by White.[1] The prognosis was from the beginning mostly described in terms of mortality and the studies were not representative for the total experience with the disease.[1–3] Beginning with the Framingham study, a more reliable view of the fate of the AP victim was presented in population studies.[4–6] Early findings indicated that high blood pressure, cardiac enlargement and pathologic findings in the resting electrocardiogram were related to an unfavorable prognosis and that a complicating myocardial infarction further increased the risk of a fatal outcome. The introduction of coronary arteriography and left ventriculography made it possible to relate the prognosis of AP to pathoanatomic changes. The more narrowed the coronary arteries and the more deranged the left ventricular

From the Section for Preventive Cardiology, Department of Medicine I, Sahlgrenska Hospital and Östra Hospital, Gothenburg University, Gothenburg, Sweden. This study was supported by grants from the Bank of Sweden Tercentenary Fund, the Swedish National Association Against Heart and Chest Diseases, Stockholm, and the Knut and Alice Wallenberg Foundation, Stockholm, Sweden. Manuscript received July 16, 1987; revised manuscript received October 21, 1987, and accepted October 23.

Address for reprints: Marianne Hagman, MD, Section for Preventive Cardiology, Department of Medicine I, Sahlgrenska Hospital, S-413 45 Gothenburg, Sweden.

function, the worse was the prognosis.[7,8] This relation also has been established in cases with mild AP and myocardial infarction without AP.[9]

The present report comprises middle-aged men with AP, derived from a random population sample, followed during more than 10 years and subjected to comprehensive prospective analyses of various possible risk indicators.

Methods

All AP cases were derived from a screening examination of men born from 1917 to 1922 and from 1924 to 1925 (ages 47 to 54 at screening), performed in Gothenburg, Sweden, and constituting a random third of the men among these age-cohorts. Some general intervention measures such as treatment of high blood pressure dietary advice for men with elevated serum cholesterol and antismoking counseling were given according to previous reports.[10,11] Patients with AP received the same advice as the other participants of the study. There was no difference in myocardial infarction or stroke incidence or total mortality between this group and the controls.[12] The present study group comprised 167 men with AP not associated with myocardial infarction (uncomplicated AP), derived from the screening examination carried out between 1971 and 1973 and 128 men with uncomplicated AP detected at rescreening 4 years later (total = 295 men).

AP was diagnosed in a multistage procedure starting with a postal questionnaire on chest symptoms (an abbreviated form of the Rose questionnaire)[13] sent to the general population and followed by an interview by a physician at a screening examination for those responding positively to questions on chest pain. Those who were found to have definite or suspected AP were examined by 1 physician who further evaluated the diagnosis and followed most of the patients for the rest of the study. Smoking habits, known diabetes mellitus, intermittent claudication, dyspnea on effort, stress and physical activity at work and during leisure time were questions asked in the questionnaire and at the interview.[11]

Smoking habits were scored as follows: (1) nonsmoker; (2) ex-smoker; (3) smoking 1 to 14 g of tobacco/day; (4) smoking 14 to 24 g; (5) smoking ≥25 g. Tobacco amount was calculated thus: 1 cigarette = 1 g of tobacco, 1 cheroot = 2 g and 1 cigar = 5 g. Experience of stress was scored from 1, meaning "never felt stress," to 6, meaning "permanent stress during the last 5 years." Physical activity was scored from 1 to 4 from lowest to highest activity at work and during leisure (both times recorded separately). Systolic and diastolic blood pressure, total serum cholesterol, body height and weight were measured at the screening examination. Relative weight was calculated as:

$$\text{Weight (kg)}/(\text{height [cm]} - 100).$$

The angina attack score was registered for each patient according to the following scoring system: (1) no chest pain; (2) single attacks; (3) some attacks per month; (4) some attacks per week; (5) daily attacks; (6) daily attacks during summer as well as winter, not only at effort but also at rest or when walking on a plane.

A screening electrocardiogram with limb leads was followed by a full 12-lead registration during the clinical examination of those judged to have definite AP or suspected AP at the screening examination. The electrocardiograms were coded according to the Minnesota code by 2 independent medical technicians.[14] At a second screening. a 12-lead electrocardiogram was performed in all and the angina cases were coded as above. The occurrence of 1 or more of the following ischemic-type changes was analyzed: Minnesota code 1:1, 1:2, 1:3, 2:1, 3:1, 3:3, 4:1–4, 5:1–3, 7:1 or 8:3, or both.

Registration of endpoints such as nonfatal myocardial infarction and cause-specific mortality was done according to a standardized procedure but without the participation of the physician associated with the care of the AP patients. A special myocardial infarction register included all nonfatal myocardial infarctions according to standardized criteria since 1968.[15] All the death certificates of the city were collected by the organization every fortnight and deaths were also checked against the official national computerized death-certificate file. Causes of death were coded by 3 physicians using the same principles but being unaware of prior diagnosis and treatment. There was a 100% completion of follow-up regarding deaths (autopsy rate: 70% of in-hospital cases and 90% of outpatients), and more than 90% completion for nonfatal

TABLE I Incidence of Fatal and Nonfatal Coronary Artery Disease Events (11.3-Year Follow-Up)

	No. of Pts	Incidence of CAD Events: No. of Pts	Incidence of CAD Events: Rate per 1,000 Person-Years	Odds Ratio Compared to "No AP or Myocardial Infarction"	95% Confidence Limits for Odds Ratio
No AP or MI	5,774	351	5.38	1.0	—
Uncomplicated AP	167	32	17.0*†	3.6	2.5–5.5
Complicated AP	58	29	44.2*	15.5	9.2–26.0
MI without AP	39	16	36.3*	10.7	5.7–20.5

* $p < 0.001$ against "No AP or myocardial infarction"; † $p < 0.001$ against "Complicated AP."
AP = angina pectoris; CAD = coronary artery disease; MI = myocardial infarction.

TABLE II Incidence of Fatal and Nonfatal Coronary Artery Disease Events (7.3-Year Follow-Up)

	No. of Pts	Incidence of CAD Events		Odds Ratio Compared to "No AP or Myocardial Infarction"	95% Confidence Limits for Odds Ratio
		No. of Pts	Rate per 1,000 Person-Years		
No AP or MI	5,265	208	5.41	1.0	—
Uncomplicated AP	128	18	19.4*	4.0	2.4–6.8
Complicated AP	34	10	40.3*	10.1	5.0–22
MI without AP	68	23	46.3*	12.4	7.5–21

* $p < 0.001$ against "No AP or myocardial infarction."
Abbreviations as in Table I.

myocardial infarction. All men were followed until March 31, 1983.

Statistics: Standard statistical methods were used to summarize and highlight all important data. Cox's regression analysis was used for the multivariate analyses. Fisher's exact test in fourfold tables was used to test the hypothesis of no difference in rates between 2 groups of patients. Pitman's nonparametric permutation test was used when testing continuous and graded variables. Only 2-tailed tests were performed and p values <0.05 were considered statistically significant.

Results

At the first examination, from 1971 to 1973, uncomplicated AP was diagnosed in 167 men and AP complicated with myocardial infarction in 58. Furthermore, another 39 men had already suffered a myocardial infarction not complicated with AP. All these subjects were followed for an average of 11.3 years and their outcome was compared with that in 5,774 men without AP or myocardial infarction (Table I). The percentage of cases suffering a fatal or nonfatal coronary artery disease (CAD) endpoint (myocardial infarction or sudden coronary death) during this time was significantly higher in the groups with AP or myocardial infarction than in the group free from CAD symptoms at entry. Those with complicated AP ran a significantly higher risk for an endpoint than those with uncomplicated AP.

At the second examination, from 1975 to 1977, AP had developed in another 162 men, 128 with uncomplicated AP and 34 with complicated AP. In addition, 68 new cases of myocardial infarction without AP had developed. All these subjects were followed for an average of 7.3 years and compared with 5,265 men without AP or myocardial infarction. Again, significantly more cases in the groups with AP or myocardial infarction reached a CAD endpoint during follow-up (Table II).

The follow-up study focused on the prognosis for men with uncomplicated AP. Among the 167 men with uncomplicated AP at first examination 32 suffered a fatal or nonfatal CAD event (11.3 year follow-up), and among the 128 subjects with uncomplicated AP at the second examination 18 had such an endpoint during follow-up (7.3-years follow-up). Thus, 50 cases in total reached a CAD endpoint.

Total mortality among those followed for 11.3 years was 19% (32 men), and for those followed for 7.3 years it was 12% (15 subjects), which was significantly higher than the percentages in those without AP or myocardial infarction: 8% for the groups followed for 11.3 years ($p < 0.001$) and 5% for those followed for 7.3 years ($p < 0.005$).

Among the 167 subjects followed for 11.3 years there were 2 variables measured at the first examination that differed significantly between the group developing a CAD endpoint and the group that did not: total serum cholesterol and systolic blood pressure (Table III). Among those who had an endpoint, 13% were receiving antihypertensive treatment compared to 4% who did not, although this difference was not significant. Among men with uncomplicated AP at the second examination the same variables were associated with risk for a CAD endpoint during follow-up (Table IV). At the second examination, 28% of those who later suffered an endpoint were receiving antihypertensive treatment compared to 22% among those who did not (the difference was not significant).

Smoking habits were not significantly associated with a CAD endpoint for any of the follow-up periods, but analyzed with a trend test for a smoking score of 1–5 an almost significant ($p = 0.058$) association was found for the follow-up period of 7.3 years.

Among the 167 men with uncomplicated AP at first screening, 152 full 12-lead electrocardiograms were available and coded (Table III). Even if all endpoint cases with missing electrocardiograms had abnormal electrocardiograms and all without endpoints and missing electrocardiograms had normal electrocardiograms, the difference would not have become significant ($p = 0.12$). At the second screening a full 12-lead electrocardiogram was performed in every subject. No significant relation between electrocardiographic changes and endpoint incidence was found (Table IV).

Scoring of AP attack frequency was missing in 5 of the 167 men with a follow-up time of 11.3 years and in 4 among the 128 men with 7.3 year follow-up. The men with mild AP (score 2–3) had a better prognosis than those with a score of 4–6 in the group with the longest

TABLE III Endpoint/Variable Relation During 11.3-Year Follow-Up

	CAD Endpoint				
	Present (n = 32)		Absent (n = 135)		p Value
Qualitative Variables	(%)		(%)		
Smokers	68		55		>0.20
Diabetes mellitus	7		5		>0.20
Intermittent claudication	41		31		>0.20
Dyspnea	56		70		>0.20
Stress score 5–6	28		32		>0.20
Physical activity					
Occupation, score 1–2	77		69		>0.20
Leisure, score 1–2	91		93		>0.20
Attack score 4–6	74		51		0.03
ECG, Minnesota code	28		22		>0.20
Quantitative Variables	mean	SD	mean	SD	p Value
Age (yrs)	51.4	1.9	51.1	1.9	>0.20
Total serum cholesterol (mg/dl)	276*	36	252*	43	0.006
Systolic blood pressure (mm Hg)	161	23	153	21	0.048
Diastolic blood pressure (mm Hg)	102	14	98	14	0.13
Relative body weight (kg/cm − 100)	1.13	0.16	1.09	0.17	>0.20
Heart rate (beats/min)	75	12	76	13	>0.20

* Corresponds to 7.18 and 6.55 mmol/liter, respectively.
ECG = electrocardiogram; SD =standard deviation; other abbreviations as in Table I.

TABLE IV Endpoint/Variable Relation During 7.3-Year Follow-Up

	CAD Endpoint				
	Present (n = 18)		Absent (n = 110)		p Value
Qualitative Variables	(%)		(%)		
Smokers	66		46		0.17
Diabetes mellitus	11		7		>0.20
Intermittent claudication	33		39		>0.20
Dyspnea	50		62		>0.20
Stress score 5–6	33		29		>0.20
Physical activity					
Occupation, score 1–2	78		67		>0.20
Leisure, score 1–2	94		94		>0.20
Attack score 4–6	70		55		>0.20
ECG, Minnesota code	33		35		>0.20
Quantitative Variables	mean	SD	mean	SD	
Age (yrs)	56.0	1.5	55.4	1.6	>0.20
Total serum cholesterol (mg/dl)	279*	39	244*	47	0.008
Systolic blood pressure (mm Hg)	164	20	146	21	0.002
Diastolic blood pressure (mm Hg)	98	12	93	12	>0.20
Relative body weight (kg/cm − 100)	1.07	0.15	1.08	0.16	>0.20
Heart rate (beats/min)	74	12	74	15	>0.20

* Corresponds to 7.25 and 6.34 mmol/liter, respectively.
ECG = electrocardiogram; SD =standard deviation; other abbreviations as in Table I.

observation time (Table III). With the trend test (score 2–6), the same significance was noted ($p = 0.025$). In the second group, followed for 7.3 years, the attack frequency had no significant relation to prognosis (Table IV).

A pooling of the 2 groups with different follow-up times—including all 295 cases with uncomplicated AP—was also performed. Systolic and diastolic blood pressures and total serum cholesterol were significantly associated with outcome at univariate analysis, and the smoking habit was close to significant ($p = 0.067$).

Analyzing the data in a different way, we looked at prognosis among patients with AP who were nonsmokers or smokers, those who had low or high attack scores, and those with serum cholesterol and systolic blood pressure in different quartiles. The results for both follow-up periods were pooled (Table V). Data for men without AP or myocardial infarction are also included. The results show that the risk is generally 2 to 3 times higher for the patients with AP for any level of the risk factors.

Systolic blood pressure was positively correlated with serum cholesterol ($p < 0.05$), and serum cholesterol was also related to attack score ($p < 0.01$). The following variables were significant in Cox regression analysis: serum cholesterol ($p = 0.0007$), systolic blood pressure ($p = 0.0035$), smoking score ($p = 0.0053$) and attack score ($p = 0.035$).

In order to study in multivariate analysis the increase of risk for a CAD endpoint with increasing levels of the individual risk factors in AP men compared with men without AP or myocardial infarction, Cox regression analyses were performed. The variable attack score was excluded because it was available only for the men with AP. The β coefficients and their standard errors for cholesterol, systolic blood pressure and smoking among men with AP were 0.0101 (±0.0011), 0.020 (±0.006), and 0.338 (±0.048), respectively. Among men without AP or myocardial infarction, these variables changed to 0.0078 (±0.0011), 0.018 (±0.002), and 0.395 (±0.048), respectively. It then became obvious that the β coefficients for each factor were similar, indicating comparable relative risk gradients when men with AP were compared with healthy subjects.

There was a negative (nonsignificant) relation between smoking and systolic blood pressure in the present series, as well as in several population studies,[16,17] and also a negative (nonsignificant) relation between smoking and attack score. These facts may explain why smoking was not a significant predictor in univariate analysis but became significant in multivariate analysis.

TABLE V Prognosis at Start of Follow-Up

Variable	AP Patients		Men Without AP or MI	
	No. of Pts	Endpoint Incidence (%)	No. of Pts	Endpoint Incidence (%)
Attack score				
2	52	10		
3	72	11		
4	91	23		
5	38	16		
6	33	24		
Smoking habits				
Nonsmoker	68	10	1,611	3
Ex-smoker	69	13	1,132	4
Smoking 1–14 g/day	94	21	2,056	8
Smoking 15–24 g/day	54	22	826	9
Smoking ≥25 g/day	8	13	144	8
Total serum cholesterol*				
Quartile 1†	91	4	2,309	3
2	70	14	1,318	5
3	71	24	1,449	7
4	62	31	966	9
Systolic blood pressure*				
Quartile 1†	83	10	2,460	3
2	73	12	1,559	5
3	70	19	1,075	8
4	68	29	998	10

Patients detected at first screening (follow-up 11.3 years) and at second screening (follow-up 7.3 years) were pooled.

* The quartile cutoff points for serum cholesterol at both the first and the second screening were 229, 253 and 285 mg/dl, respectively (= 5.95, 6.75 and 7.41 mmol/liter), for systolic blood pressure at the first screening: 140, 154 and 168 mm Hg, respectively, and at the second screening: 134, 148, and 161 mm Hg, respectively.

† The quartile cutoff levels were calculated for the AP patients; that is why the numbers for men without AP or myocardial infarction differ between "quartiles."

Abbreviations as in Table I.

Discussion

Risk factors for CAD have been described in many studies.[6,12,16,17] During recent years, when sufficiently large population groups have been followed for sufficiently long periods, it has become evident that the risk factor pattern may differ between myocardial infarction and AP.[11,17] It also has been found that the "secondary" risk factors (or prognostic factors) *after* a myocardial infarction are different from those before such an event, at least during the first years. Thus, it has repeatedly been found that factors indicating large myocardial damage, number of infarcts and ventricular arrythmias are important prognostic factors during the first 3 to 4 years following the myocardial infarction.[18,19] However, when this period has passed, the "primary" risk factors seem to resume their importance, and elevated serum cholesterol, elevated blood pressure, tobacco smoking and diabetes become long-term prognostic factors.[20,21]

Several follow-up studies have shown that the number of diseased vessels and lesions in critical segments, such as the left main stem, as well as the signs of ventricular dysfunction (often unknown clinically), have important prognostic implications among AP patients and that corrections by means of coronary surgery may improve the prognosis considerably.[22–24] The importance of the myocardial factor becomes evident in the present study, when it shows that the incidence of CAD events among those who had a complicated AP was more than twice that of subjects who had an uncomplicated AP. Men with uncomplicated AP had a CAD event rate 3 times higher than that of men who were initially free from myocardial infarction or AP.

In population studies, all patients with varying degrees of symptoms have been included, ranging from those with minor symptoms (such that would not give rise to further diagnostic investigations), to those with severe symptoms (similar to the symptoms of patients included in angiographic series). Nowadays, many middle-aged men with AP may have undergone bypass surgery before inclusion in a population survey and thus bias the study sample. None of the present subjects had undergone bypass surgery before inclusion in the study. As it would not be ethically, clinically or economically justifiable to perform coronary angiography in all the patients in the present study, we were unable to determine the extent of the coronary artery lesions and their significance for prognosis. The relation to the attack score may, however, be taken as an indication of how important the degree of CAD is for prognosis.

One has to be cautious when drawing conclusions from studies like ours because of the relatively small number of endpoints: 50 CAD endpoints were available for study for the 2 periods with a total of 295 patients. This can be compared with a similar follow-up study performed on the Framingham data, in which 53 out of 130 men with uncomplicated AP experienced coronary attacks at a rate of 48.6/1,000 person-years of follow-up.[25] Such a number of endpoints is comparable to the present study but the incidence per 1,000 patient-years is more than double. To a large extent this difference may be explained by the much higher age of the subjects in the Framingham study. Our results are concurrent with the results of the Framingham Study[25] regarding blood pressure, but they did not find that high serum cholesterol was a significant risk factor even though the risk was somewhat higher among those with high cholesterol levels.

It is notable that high blood pressure was associated with a worse prognosis even though hypertensive men were treated when they were detected in the present study. In the total study sample comprising 7,495 men, the 5.9% prevalence of treated hypertension at the start of the study had increased to 26% after 10 years.[12] It would have been of interest to see whether more intensive blood pressure treatment also would have caused reduction (or increase) of the endpoint incidence, but such an analysis was not possible because of the small number of patients with AP and the fact that patients were not randomized to treatment. However, another analysis of the total sample of patients under antihypertensive treatment indicated that the degree of blood pressure reduction did not appreciably reduce endpoint incidence, whereas the prognosis

was positively affected by reductions of total serum cholesterol and smoking.[26]

Pathologic electrocardiographic findings have been of prognostic importance for AP patients in some studies,[23,25,27] but not in another.[9] Our findings concerning attack frequency are similar to those of the Whitehall study.[6] Patients with more severe AP had a worse prognosis, although this tendency has not been a consistent finding.[28]

In conclusion, we found that prognosis among patients with uncomplicated AP, in addition to attack score, was strongly dependent on the conventional risk factors for hard CAD events such as elevated serum cholesterol, elevated blood pressure and smoking habits. The findings indicate that preventive measures against these factors seem to be equally important for subjects with AP, clinically healthy subjects and patients with various manifestations of atherosclerosis.

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Assessment of Mitral Flow Velocity with Exercise by an Index of Stress-Induced Left Ventricular Ischemia in Coronary Artery Disease

GEORGE D. MITCHELL, MD, RICHARD C. BRUNKEN, MD, MARKUS SCHWAIGER, MD, BRYAN C. DONOHUE, MD, JANINE KRIVOKAPICH, MD, and JOHN S. CHILD, MD

Exercise-induced myocardial ischemia results in both diastolic and systolic left ventricular (LV) dysfunction. To investigate the utility of Doppler assessment of LV diastolic function with exercise, 28 consecutive patients underwent digital stress echocardiography, including measurement of mitral flow velocity by pulsed-wave Doppler and simultaneous stress thallium imaging. The mean mitral flow velocity was measured as the integrated area under the LV diastolic inflow Doppler spectral display. The change in mean mitral flow velocity from baseline to immediate postexercise was compared among 3 patient groups: (1) patients with thallium redistribution or exercise-induced wall-motion abnormalities, or both, consistent with exercise-induced ischemia (n = 18), (2) patients with no evidence of stress-induced ischemia, with or without resting wall-motion abnormalities (n = 10), and (3) 10 control subjects of similar age with normal resting 12-lead electrocardiograms, normal resting and postexercise 2-dimensional echocardiograms and normal electrocardiographic treadmill stress testing. The percent increase in mean mitral flow velocity was 101% (±59) for controls and 86% (±53) for patients without stress-induced ischemia versus 33% (±24) in patients with stress-induced ischemia ($p < 0.005$). An increase in mean mitral flow velocity with exercise of >50% correctly identified 9 of 10 nonischemic control patients. An increase in mean velocity of <50% predicted ischemia in 15 of 18 patients with evidence of stress-induced ischemia ($p < 0.005$) Thus, Doppler assessment of LV diastolic function with exercise expressed as a change in the mean velocity of mitral flow is a useful indicator of stress-induced ischemia.

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Studies have shown that exercise-induced myocardial ischemia can produce abnormalities in both diastolic and systolic left ventricular (LV) function.[1-5] Several methods have been used to assess diastolic function, including frame by frame analysis of contrast ventriculograms to determine rates of diastolic filling and analysis of time-activity curves obtained by gated blood pool scintigraphy to obtain filling rates and filling fractions. These methods are not easily applied to the study of large numbers of patients or serial assessment of individual patients. Doppler echocardiography is a noninvasive means of obtaining beat by beat analysis of LV diastolic filling.[6-10] The characteristics of the Doppler spectral display of diastolic transmitral flow velocity have been studied in patients with systemic hypertension, dilated cardiomyopathy, acute myocardial infarction and during percutaneous transluminal coronary angioplasty.[11-16] Rassi et al[17] have shown in normal subjects undergoing supine bicycle exercise that the mean mitral flow velocity increased by more than 100% from baseline to peak exercise. Changes in transmitral flow occurring with exercise in patients with coronary artery disease have not been well described. This study investigates the usefulness of Doppler assessment of LV diastolic function during stress testing in patients with known or suspected coronary artery disease as a possible marker of exercise-induced ischemia.

From the Department of Medicine, Division of Cardiology, and the Department of Radiology, Division of Nuclear Medicine, UCLA School of Medicine, Los Angeles, California. Manuscript received July 24, 1987; revised manuscript received and accepted October 29, 1987.

Dr. Mitchell's present address: Baystate Medical Center, Springfield, Massachusetts.

Address for reprints: George D. Mitchell, MD, Cardiology Service, Baystate Medical Center, 759 Chestnut Street, Springfield, Massachusetts 01199.

Methods

Patients: A total of 28 consecutive patients referred to the UCLA noninvasive cardiology laboratory for treadmill stress testing underwent simultaneous digi-

tal stress echocardiography and stress thallium imaging. The "ischemic" group (group 1) comprised 18 patients with exercise-induced wall-motion abnormalities, exercise-induced thallium perfusion defects, or both. The "nonischemic" group (group 2) included 10 patients without exercise-induced wall motion abnormalities and negative thallium scans. Since the time of initiation of stress echocardiography in this laboratory, a total of 10 patients undergoing digital stress echocardiography with measurement of transmitral flow velocity had normal results in their resting 12-lead electrocardiograms, resting and postexercise 2-dimensional echocardiograms and electrocardiographic treadmill stress testing. These patients, whose ages were similar to those of the study patients, constituted the control group (group 3).

Echocardiography: Resting and immediate postexercise 2-dimensional echocardiographic imaging was performed on supine subjects with a Hewlett-Packard 77020A echocardiographic recorder with a 2.5 MHz electronically phased array transducer with pulsed Doppler (2.0 MHz) capability. Optimal windows for obtaining parasternal and apical views at rest were clearly marked on each patient's chest wall. Immediate postexercise 2-dimensional echocardiographic images were obtained in all cases within 30 to 60 seconds of termination of upright treadmill exercise. Digitized cine loops of 2-dimensional echocardiographic images obtained using the apical 4-chamber, 2-chamber and long axis views and the parasternal short axis view were made on a Microsonics digitizing system. Each apical view was divided into 6 segments.[18] Wall-motion analysis was performed independently by 2 observers unaware of other patient data using a grading system from −1 for dyskinesia to 4 for hyperkinesia. Discrepancies between observers were resolved by consensus review. The development of a new exercise-induced wall-motion abnormality was defined as >1 grade deterioration in wall-motion score for any 1 segment from baseline to immediate postexercise. The development of dyskinesia in an area of prior akinesia was not considered a new wall-motion abnormality.

Doppler: The time-velocity profile of transmitral flow by pulsed Doppler was obtained with the sample volume placed on the ventricular side of the mitral anulus near the tips of the mitral leaflets. Beats used for analysis were those that showed the greatest mitral peak flow velocity regardless of the phase of respiration. Four parameters of LV filling were obtained from the analysis of the time-velocity spectral display: (1) peak velocity in early diastole; (2) peak velocity during atrial systole; (3) ratio of early diastolic peak flow velocity to peak flow velocity during atrial systole; (4) mean mitral flow velocity—obtained by digitizing the contour of the darkest outline of the spectral display of the transmitral time-velocity profile (Figure 1). Digitization was performed using a standard, commercially available, digitizing pad from Trinity Systems. The integrated area under the curve was expressed as the mean mitral flow velocity. The integrated area under the spectral envelope (mean mitral flow velocity) normalized for the diastolic filling period was expressed as the time-velocity integral. Pulsed Doppler measurements were obtained immediately after 2-dimensional echocardiographic imaging at baseline and upright treadmill exercise.

Thallium imaging: Stress thallium imaging was performed after obtaining echocardiographic studies immediately after exercise. Thallium images (64 of 20) were obtained using a Siemens Orbiter—SPECT system CLC 7500S. Redistribution images were obtained 4 hours after exercise. Those thallium perfusion defects present immediately after exercise and exhibiting redistribution 4 hours later were considered to represent exercise-induced myocardial ischemia. Thallium studies were read by consensus of 2 observers blinded to other patient data.

Statistical methods: Independent sample 2-tailed Wilcoxon rank sum tests for unpaired data were performed. Differences between means of more than 2 groups were evaluated by 1-way analysis of variance. 2 × 2 contingency tables were analyzed using the 2-tailed Fisher's exact test. Values are reported as mean ± standard deviation. A probability value <0.05 was considered to be significant.

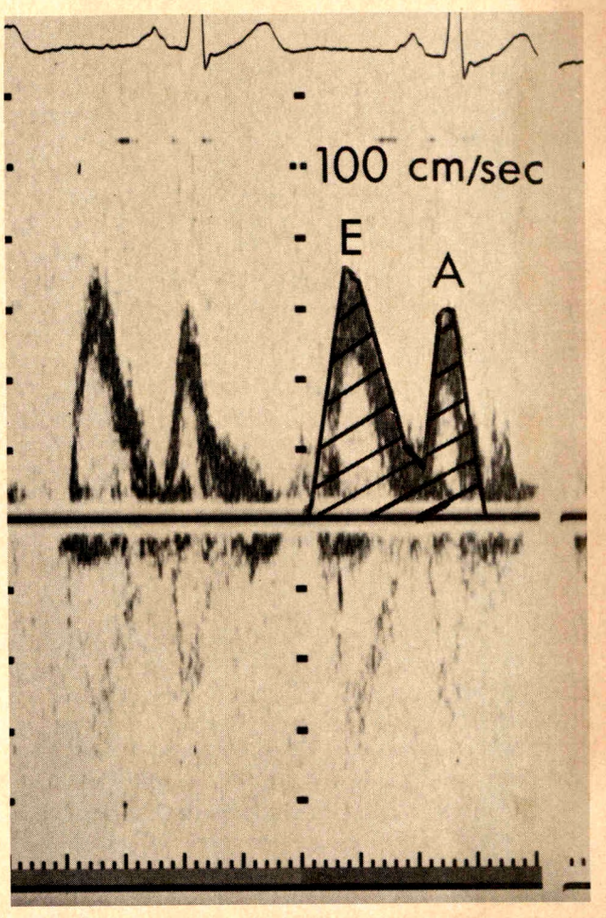

FIGURE 1. Sample spectral display of Doppler transmitral flow velocity. E = peak velocity in early diastole; A = peak velocity during atrial systole; integrated area under the darkest outline of the spectral display = mean mitral flow velocity.

Results

A summary of the overall results of simultaneous digital stress echocardiography and stress thallium imaging performed in the 28 consecutive patients with known or suspected coronary artery disease undergoing treadmill stress testing is shown in Figure 2. The 18 patients constituting the "ischemic group" (group 1) comprised 12 with positive SPECT thallium scan results (group 1A) and 6 with negative thallium scan findings but with exercise-induced wall-motion abnormalities (group 1B). Of the 10 patients with "nonischemic" studies (group 2), 7 had resting wall-motion abnormalities (Group 2A). For the 3 groups undergoing comparison, their mean ages (63 ± 10, 55 ± 12 and 55 ± 14 years for groups 1, 2 and 3, respectively), baseline heart rates (69 ± 18, 67 ± 12 and 61 ± 9 beats/min), postexercise heart rates (88 ± 23, 98 ± 20 and 91 ± beats/min), percentage of maximum predicted heart rates at peak exercise (81 ± 15, 87 ± 13 and 88 ± 12%), and double-products achieved (21,000 ± 5,000, 25,000 ± 7,000 and 25,000 ± 6,000 mm Hg · beats/min) were comparable. The number of patients in each group with a history of hypertension (8 of 18 in group 1, 3 of 10 in group 2 and 3 of 10 in group 3) was similar ($p = 0.9$). There was a trend toward greater use of calcium antagonists or β-blocking drugs in groups 1 and 2 (9 of 18 and 6 of 10, respectively), compared with group 3 (2 of 10) ($p = 0.2$).

Mean mitral flow velocities at baseline and after exercise for each of the patient groups are listed in Table I. In controls, the mean mitral flow velocity doubled, whereas patients with exercise-induced ischemia had an increase in mean mitral flow velocity of only 33% ($p < 0.005$). Sample Doppler tracings in a control and in an ischemic patient are shown in Figure 3. There was no difference between controls and patients with nonischemic studies despite the fact that 70% of the nonischemic patients had resting wall-motion abnormalities. There was no difference in the response of the mean mitral flow velocity with exercise between the group with positive thallium scan results and the group with exercise-induced wall-motion abnormalities and negative thallium scan results.

An increase in mean mitral flow velocity of >50% with exercise correctly identified 9 of 10 controls as nonischemic. The absence of a >50% increase in mean mitral flow velocity predicted an ischemic response in 15 of 18 patients with exercise-induced ischemia ($p < 0.005$). The number of patients demonstrating the proposed control response among those with nonischemic studies was similar to that among controls.

The time-velocity integral was obtained by dividing each mean mitral flow velocity by the diastolic filing period (duration of total transmitral flow). Baseline, postexercise and percent change in time-velocity integrals and diastolic filling periods for the 3 patient

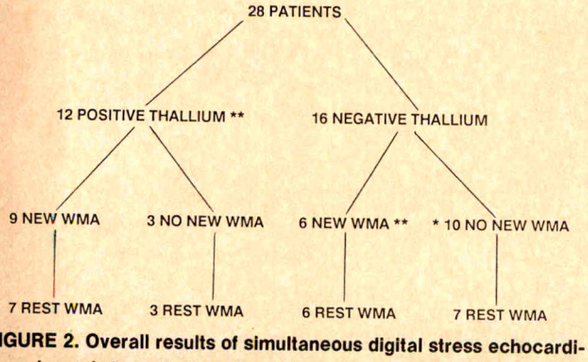

FIGURE 2. Overall results of simultaneous digital stress echocardiography and stress thallium imaging in 28 consecutive patients with known or suspected coronary after coronary artery disease. * nonischemic group; ** ischemic group. WMA = wall-motion abnormality.

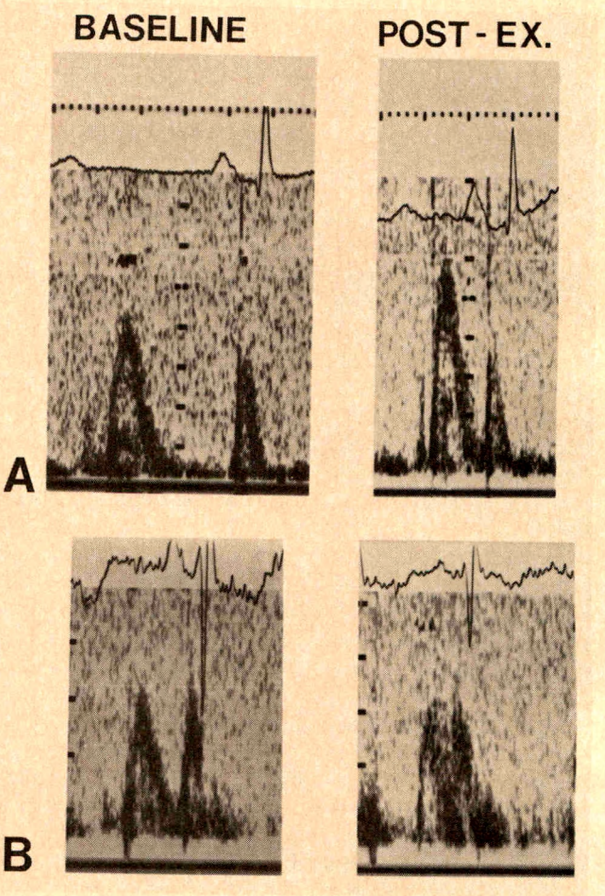

FIGURE 3. Preexercise and postexercise spectral display of Doppler transmitral flow velocity in 2 representative patients. *A*, control: a 61-year-old female, 13-minute total exercise time on Bruce protocol, reached 88% maximal predicted heart rate, double-product = 23,800, baseline mean mitral flow velocity = 33 cm/s, postexercise mean mitral flow velocity = 67 cm/s (103% increase). *B*, thallium redistribution and exercise wall-motion abnormality developed in this 58-year-old male, 11.5-minute total exercise time on Bruce protocol, reached 100% maximal predicted heart rate, double-product = 27,200, baseline mean mitral flow velocity = 42 cm/s, postexercise mean mitral flow velocity = 53 cm/s (26% increase). Each division = 20 cm/s.

TABLE I Mitral Flow Velocity Data

Pt Group	Baseline Mitral Flow Velocity (cm/s)	Postexercise Mitral Flow Velocity (cm/s)	Percent Change in Mitral Flow Velocity* (cm/s)	Patients with >50% Increase in Mitral Flow Velocity* (cm/s)
1	39 ± 13	51 ± 18	33 ± 24	3/18
1A	42 ± 15	56 ± 20	31 ± 29	2/12
1B	32 ± 6	41 ± 9	34 ± 24	1/6
2	33 ± 7	59 ± 12	86 ± 53	8/10
2A	35 ± 7	63 ± 10	90 ± 64	5/7
3	31 ± 7	60 ± 12	101 ± 59	9/10

All values are mean ± standard deviation.
* p = <0.005 between groups.

TABLE II Diastolic Filling Period and Time-Velocity Integral Data

Pt Group	Baseline DFP	Postexercise DFP	Percent Change in DFP	Baseline TVI	Postexercise TVI	Percent Change in TVI
1	0.48 ± 0.16	0.37 ± 0.15	23 ± 16	18 ± 5	17 ± 4	−1 ± 18
2	0.48 ± 0.11	0.29 ± 0.06	37 ± 14	16 ± 4	17 ± 4	13 ± 23
3	0.59 ± 0.13	0.34 ± 0.09	40 ± 18	17 ± 4	20 ± 4	11 ± 17
	NS	NS	p = 0.02	NS	NS	NS

All values are in mean ± standard deviation.
DFP = diastolic filling period (in seconds of diastole/beat); NS = not significant; TVI = time-velocity integral.

groups are listed in Table II. The percent change in time velocity integral from baseline to postexercise was no different among the 3 groups. The percent decrease in diastolic filling period was less for the ischemic group than either controls or patients with nonischemic studies (p = 0.02), despite similar heart rates at baseline and postexercise. The ratios of peak velocity in early diastole to peak velocity during atrial systole (E/A ratios), were no different among the patient groups at baseline or postexercise. The percent change in this parameter from baseline to postexercise did not differ among the 3 groups.

Discussion

Recent interest has focused on the use of Doppler velocity measurements to assess global LV function. Aortic and transmitral flow velocity determinations combined with anular cross-sectional area measurements have been used to attempt to estimate stroke volume and cardiac output.[19,20] The response of aortic flow velocity to exercise has been extensively studied.[21–23] Little is known of the response of transmitral flow to upright treadmill exercise in normal subjects or patients with coronary artery disease. This study corroborates the increase in transmitral flow velocity seen by Rassi et al[17] in normal subjects, by showing a similar increase of at least 100% in controls after treadmill exercise. It also demonstrates an abnormal response of the velocity of transmitral flow with exercise in patients with noninvasive evidence of stress-induced myocardial ischemia. The failure in ischemic patients to increase transmitral flow velocity with exercise to the extent seen in controls or nonischemic patients may be a reflection of ischemia-induced compromise of stroke volume, LV filling, or both. The change from baseline to postexercise in the time-velocity integral, which relates more directly to total transmitral flow than mean velocity alone, was not significantly different among the 3 study groups. Although given the small number of patients the likelihood of beta error must be considered, this would suggest that changes in stroke volume were not significantly different and that an abnormal response of mean mitral flow velocity with exercise in ischemic patients more likely represents an ischemia-induced change in LV compliance and, therefore, resistance to filling. Likewise, the smaller percent decrease in diastolic filling period from baseline to postexercise in ischemic patients may reflect a relative prolongation of the diastolic filling period due to ischemia-induced decrease in LV compliance.

The changes in the mean velocity of transmitral flow with exercise were similar in controls and patients without evidence of exercise-induced ischemia, even though 7 of 10 patients in this nonischemic group had resting wall-motion abnormalities on 2-dimensional echocardiography. When considered separately, these 7 patients with presumably nonischemic but infarcted hearts had quite similar increases in transmitral flow with exercise compared with controls. This would suggest that the abnormal response of transmitral flow velocity with exercise (i.e., failure to increase by at least 50%) may be a marker of exercise-induced ischemia rather than merely a marker of resting LV compliance abnormalities related to prior ischemic injury.

Because baseline, postexercise and percent of maximum predicted heart rates were all similar, the differences noted between groups in the response of mean mitral flow velocity to exercise are not a result of differences in heart rate. Likewise, the degree of stress induced was similar, as there was no difference between groups in double-product achieved. Changes in the pattern of LV filling by pulsed Doppler may occur with aging.[24-26] The control group used in this study was of an age distribution similar to the ischemic and nonischemic groups. Hypertension and therapy with calcium antagonists or β-blocking drugs can affect LV compliance. There was no significant difference between groups in the incidence of hypertension. Although there was a trend toward more frequent use of β-blockers or calcium antagonists in the ischemic and nonischemic groups, as compared with controls, this difference did not reach statistical significance. The effect of these agents on diastolic LV function would be to increase myocardial compliance, which would theoretically improve transmitral flow and, therefore, would not account for the differences shown. Regardless, each patient served as his or her own control for the comparison of rest versus immediate postexercise mitral flow velocities.

The peak velocity in early diastole (E) and peak velocity during atrial systole (A), obtained by pulsed Doppler, and their ratio (E/A ratio), have been studied in normal subjects and in various forms of acquired heart disease. The absolute values for the E/A ratio and the percent changes in E/A ratio from baseline to postexercise were no different between patient groups. With increased heart rates after exercise, it was noted that the E and A velocities tended to fuse, making separate determination of E and A velocity integrals technically difficult. The mean velocity of transmitral flow, which takes into account the velocities in early diastole and during atrial systole, would appear to be a more reliable and reproducible measure of Doppler-derived changes in transmitral flow with exercise.

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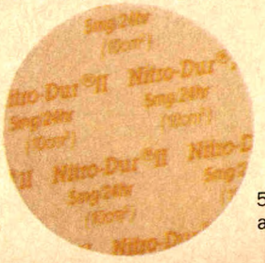

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BRIEF SUMMARY

INDICATIONS AND USAGE: This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia.

WARNINGS: The NITRO-DUR II system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

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PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced or use of the product discontinued. NITRO-DUR II is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with NITRO-DUR II. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NITRO-DUR II is administered to a nursing woman.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing NITRO-DUR II therapy. If headache persists, the NITRO-DUR II dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the NITRO-DUR II dosage should be reduced or use of the product discontinued.

CAUTION: Federal law prohibits dispensing without prescription. For complete prescribing information, please see package insert.

EDP #I030150 Revised 0585

All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA.

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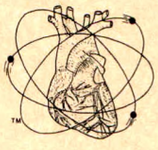

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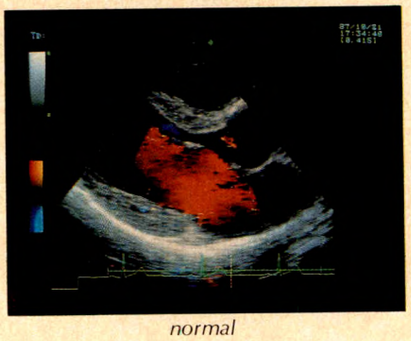

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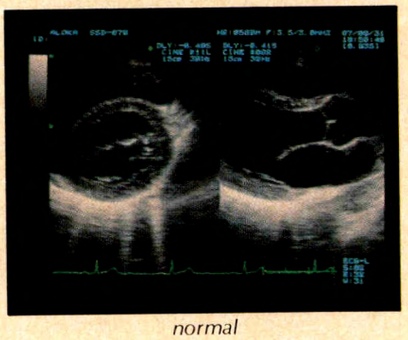

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  Side effects generally were mild and transient. Dizziness and asthenia were the most common. Others reported significantly more frequently than with placebo were nasal congestion, peripheral edema, somnolence, nausea, palpitations, and blurred vision. Incidence of syncope (1.0%) was not significantly different from placebo.

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Please see accompanying brief summary.
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HYTRIN®

(terazosin hydrochloride tablets)

Brief Summary

CLINICAL PHARMACOLOGY: Pharmacodynamics: Clinical studies of terazosin used in once-a-day (majority) and b.i.d regimens with total doses usually in the range of 5-20mg/day, in patients with mild or moderate hypertension. Because terazosin, like all alpha antagonists, can cause large falls in blood pressure after the first dose or first few doses, the initial dose was 1mg in virtually all studies, with subsequent titration to a specified fixed dose or titration to a specified blood pressure end point.

Blood pressure responses were measured at the end of the dosing interval (usually 24 hrs.) and effects were shown to persist throughout the interval, with usual supine responses 5-10mmHg systolic and 3.5-8mmHg diastolic greater than placebo. The responses in the standing position tended to be somewhat larger, although this was not true in all studies. The magnitude of blood pressure responses was similar to prazosin and less than hydrochlorothiazide (in a single study). In measurements 24 hrs. after dosing, heart rate was unchanged.

Limited measurements of peak response (2-3 hrs. after dosing) during chronic terazosin administration indicate that it is more than twice the trough (24 hr.) response, suggesting some attenuation of response at 24 hrs., presumably due to a fall in blood terazosin concentrations at the end of the dose interval. This explanation is not established with certainty and is not consistent with the similarity of blood pressure response to once-a-day and b.i.d. dosing. With the absence of an observed dose-response relationship over a range of 5-20mg, i.e., if blood concentrations fall to the point of providing less than full effect at 24 hrs., a shorter dosing interval or larger dose should lead to increased response. Measure blood pressure (BP) at the end of the dose interval; if response is not satisfactory, patients may be tried on a larger dose or b.i.d. regimen. The latter should be considered if side effects, such as dizziness, palpitations, or orthostatic complaints, are seen within a few hours after dosing.

The greater BP effect associated with peak plasma concentrations (first few hours after dosing) appears somewhat more position-dependent (greater in the erect position) than the effect of terazosin at 24 hrs. In the erect position there is a 6-10 bpm increase in heart rate in the first few hours after dosing. During the first 3 hrs. after dosing 12.5% of patients had a systolic pressure fall of 30mmHg or more from supine to standing, or standing systolic pressure below 90mmHg with a fall of at least 20mmHg, compared to 4% of a placebo group.

INDICATIONS AND USAGE: Indicated for the treatment of hypertension.

CONTRAINDICATIONS: None known.

WARNINGS: Syncope and "First-dose" Effect: Terazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially postural hypotension, and syncope in association with the first dose or first few doses. A similar effect may occur if therapy is interrupted for more than a few doses. Syncope has been reported with other alpha-adrenergic blocking agents in association with rapid dosage increases or introduction of another antihypertensive drug. Syncope may be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by severe supraventricular tachycardia with heart rates of 120-160 bpm.

To decrease the likelihood of syncope or excessive hypotension, always initiate treatment with a 1mg dose at bedtime. The 2mg and 5mg tablets are not indicated as initial therapy. Increase dosage slowly, and add additional antihypertensive agents with caution. Caution patients to avoid situations where injury could result if syncope occurs during initiation of therapy.

In early studies, where increasing single doses up to 7.5mg were given at 3 day intervals, tolerance to the first dose phenomenon did not necessarily develop and the "first dose" effect was observed at all doses. Syncopal episodes occurred in 3 of 14 subjects given doses of 2.5, 5, and 7.5mg, which are higher than the recommended initial dose. Severe orthostatic hypotension (BP 50/0mmHg) was seen in two others and dizziness, tachycardia, and lightheadedness occurred in most subjects. These adverse effects all occurred within 90 min. of dosing.

In multiple dose clinical trials involving nearly 2000 patients, syncope was reported in about 1% of patients, in no case severe or prolonged, and was not necessarily associated with early doses.

If syncope occurs, place patient in recumbent position and treat supportively. There is evidence that the orthostatic effect of terazosin is greater, even in chronic use, shortly after dosing.

PRECAUTIONS: *General: **Orthostatic Hypotension:*** While syncope is the most severe orthostatic effect of terazosin, other symptoms of lowered BP, such as dizziness, lightheadedness and palpitations, are more common, occurring in 28% of patients in clinical trials. Patients with occupations in which such events represent potential problems should be treated with particular caution.

Information for Patients: Make aware of possibility of syncopal and orthostatic symptoms, especially at initiation of therapy, and to avoid driving or hazardous tasks for 12 hrs. after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. Caution to avoid situations where injury could result should syncope occur during initial therapy. Advise to sit or lie down when symptoms of lowered BP occur and to rise carefully from a sitting or lying position. Bothersome dizziness, lightheadedness, or palpitations should be reported to physician.

Tell patients that drowsiness or somnolence can occur, requiring caution in people who must drive or operate heavy machinery.

Laboratory Tests: Small but statistically significant decreases in hematocrit, hemoglobin, WBC, total protein and albumin were observed in clinical trials. The magnitude of decreases did not worsen with time. These findings suggest the possibility of hemodilution.

Drug Interactions: In controlled trials, terazosin was added to diuretics, and several beta-adrenergic blockers; no unexpected interactions were observed. Terazosin has also been used concomitantly without interaction in at least 50 patients on the following: 1) analgesic/anti-inflammatory (acetaminophen, aspirin, codeine, ibuprofen, indomethacin); 2) antibiotics (erythromycin, trimethoprim and sulfamethoxazole); 3) anticholinergic/sympathomimetics (phenylephrine HCl, phenylpropanolamine HCl, pseudoephedrine HCl); 4) antigout (allopurinol); 5) antihistamines (chlorpheniramine); 6) cardiovascular agents (atenolol, hydrochlorothiazide, methyclothiazide, propranolol); 7) corticosteroids; 8) gastrointestinal agents (antacids); 9) hypoglycemics; 10) sedatives and tranquilizers (diazepam).

Carcinogenesis, Mutagenesis, Impairment of Fertility: HYTRIN was devoid of mutagenic potential when evaluated *in vivo* and *in vitro*.

HYTRIN, administered in feed to rats at doses of 8, 40, and 250mg/kg/day for 2 yrs., was associated with a statistically significant increase in benign adrenal medullary tumors of male rats exposed to the 250mg/kg dose. This dose is 695 X max. recommended human dose (20mg/55kg). Female rats were unaffected. HYTRIN was not oncogenic in mice when administered in feed for 2 yrs. at a maximum tolerated dose of 32mg/kg/day.

The absence of mutagenicity in a battery of tests, of tumorigenicity of any cell type in the mouse carcinogenicity assay, of increased total tumor incidence in either species, and of proliferative adrenal lesions in female rats, suggests a male rat species-specific event. Numerous other diverse pharmacological and chemical compounds have been associated with these tumors in male rats without supporting evidence for carcinogenicity in man.

Effects on fertility were assessed in a standard fertility/reproductive performance study in which male and female rats were administered oral doses of 8, 30 and 120mg/kg/day. Four of 20 male rats given 30mg/kg and 5 of 19 male rats given 120mg/kg failed to sire a litter. Testicular weights and morphology were unaffected. Vaginal smears at 30 and 120mg/kg/day appeared to contain less sperm than smears from control matings and good correlation was reported between sperm count and subsequent pregnancy.

Oral use for 1 or 2 yrs. elicited a statistically significant increase in testicular atrophy in rats exposed to 40 and 250mg/kg/day, but not in rats exposed to 8mg/kg/day (> 20 X max. recommended human dose). Testicular atrophy was observed in dogs dosed with 300mg/kg/day (> 800 X max. recommended human dose) for 3 months but not after 1 yr. when dosed with 20mg/kg/day. This lesion has also been seen with Minipress®.

Pregnancy: Teratogenic effects: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women and the safety of terazosin in pregnancy has not been established. HYTRIN is not recommended during pregnancy unless potential benefit justifies potential risk to mother and fetus.

Nonteratogenic effects: In a peri- and post-natal development study in rats, significantly more pups died in the group dosed with 120mg/kg/day (> 300 X max. recommended human dose) than in the control group during the 3-week post-partum period.

Nursing Mothers: It is not known whether terazosin is excreted in breast milk; therefore, exercise caution when administering terazosin to a nursing woman.

Pediatric Use: Safety and effectiveness have not been determined.

ADVERSE REACTIONS: The prevalence of adverse reactions has been ascertained from 14 placebo-controlled studies conducted primarily in the U.S. The studies involved once-a-day administration of terazosin as monotherapy or in combination with other antihypertensive agents, at doses ranging from 1 to 40mg. All adverse events reported during these studies were recorded as adverse reactions. Adverse events where the prevalence rate in the terazosin group was at least 5%, where the prevalence rate for the terazosin group was at least 2% and was greater than the prevalence rate for the placebo group, or where the reaction is of particular interest are summarized below. Only asthenia, blurred vision, dizziness, nasal congestion, nausea, peripheral edema, palpitations and somnolence were significantly ($p < 0.05$) more common in patients receiving terazosin than in patients receiving placebo. Other events include **[%TERAZOSIN-%PLACEBO]**: asthenia (11.3%-4.3%), back pain (2.4%-1.2%), blurred vision (1.6%-0%), depression (0.3%-0.2%), dizziness (19.3%-7.5%), dyspnea (3.1%-2.4%), edema (0.9%-0.6%), headache (16.2%-15.8%), impotence (1.2%-1.4%), libido decreased (0.6%-0.2%), nasal congestion (5.9%-3.4%), nausea (4.4%-1.4%), nervousness (2.3%-1.8%), pain-extremities (3.5%-3%), palpitations (4.3%-1.2%), paresthesia (2.9%-1.4%), peripheral edema (5.5%-2.4%), postural hypotension (1.3%-0.4%), sinusitis (2.6%-1.4%), somnolence (5.4%-2.6%), tachycardia (1.9%-1.2%), weight gain (0.5%-0.2%).

Adverse reactions were usually mild or moderate in intensity but sometimes were serious enough to interrupt treatment. Adverse reactions that were most bothersome as judged by being reported as reasons for discontinuation of therapy by at least 0.5% of the terazosin group and being reported more often than in the placebo group **[%TERAZOSIN-%PLACEBO]** are: asthenia (1.6%-0%), blurred vision (0.6%-0%), dizziness (3.1%-0.4%), dyspnea (0.9%-0.6%), headache (1.3%-1%), nasal congestion (0.6%-0%), nausea (0.8%-0%), palpitations (1.4%-0.2%), paresthesia (0.8%-0.2%), peripheral edema (0.6%-0%), postural hypotension (0.5%-0%), somnolence (0.6%-0.2%), syncope (0.5%-0.2%), tachycardia (0.6%-0%).

Additional adverse reactions have been reported, but these are not distinguishable from symptoms that might have occurred in the absence of exposure to terazosin. The following additional adverse reactions were reported by at least 1% of 1987 patients who received terazosin in clinical studies or during marketing experience: abdominal pain, abnormal vision, anxiety, arrhythmia, arthralgia, arthritis, bronchitis, chest pain, cold symptoms, conjunctivitis, constipation, diarrhea, dry mouth, dyspepsia, epistaxis, facial edema, fever, flatulence, flu symptoms, gout, increased cough, insomnia, joint disorder, myalgia, neck pain, pharyngitis, pruritus, rash, rhinitis, shoulder pain, sweating, tinnitus, urinary frequency, urinary tract infection, vasodilation, vomiting.

DOSAGE AND ADMINISTRATION: Dose and dose interval (12 or 24 hrs.) should be adjusted according to BP response.

Initial Dose: 1mg at bedtime. Observe the initial dosing regimen strictly to minimize potential for severe hypotensive effects.

Subsequent Doses: Slowly increase dose to achieve desired BP response. Usual dose range is 1mg to 5mg once a day. Some patients may benefit from doses up to 20mg/day. Doses over 20mg do not appear to provide further BP effect. Doses over 40mg have not been studied. Monitor BP at the end of dosing interval to assure control is maintained. It may be helpful to measure BP 2-3 hrs. after dosing to see if maximum and minimum responses are similar, and to evaluate symptoms which can result from excessive hypotensive response. If response is substantially diminished at 24 hrs. consider an increased dose or b.i.d. regimen. **If administration is discontinued for several days or longer, reinstitute therapy using initial dosing regimen.** In clinical trials, except for the initial dose, the dose was given in the morning.

Use With Other Drugs: Caution should be observed when terazosin is administered concomitantly with other antihypertensive agents (e.g., calcium antagonists) to avoid the possibility of significant hypotension. When adding a diuretic or other antihypertensive agent, dosage reduction and retitration may be necessary.

August, 1987 **Abbott Health Care Products, Inc.** North Chicago, IL 60064 7083834

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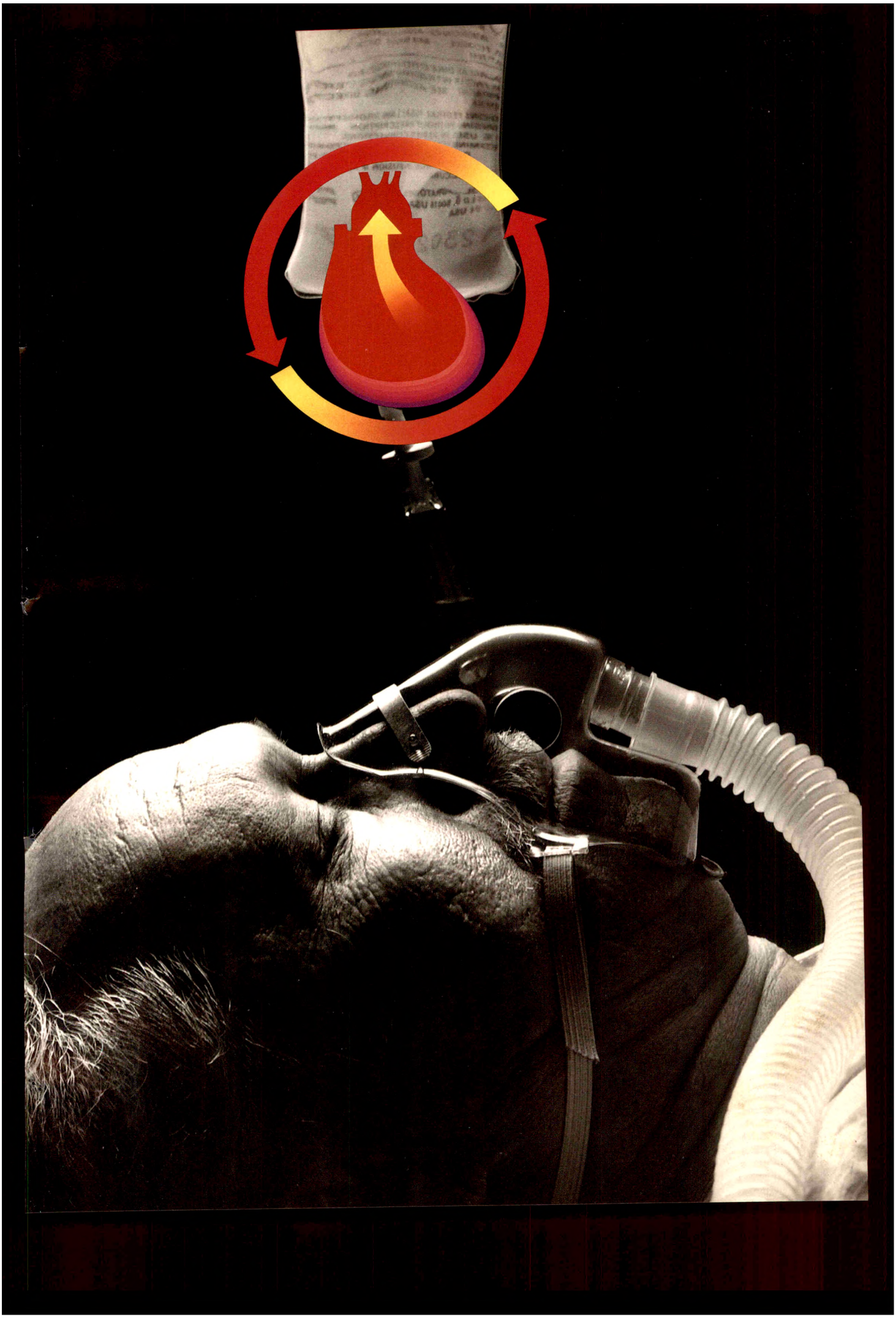

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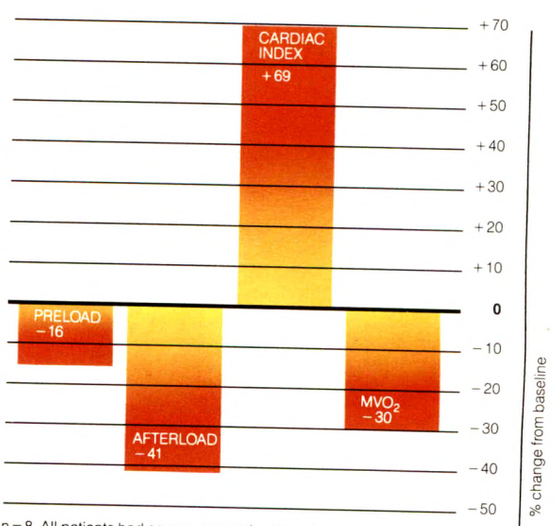

n = 8. All patients had severe congestive heart failure due to coronary artery disease. Amrinone was infused at 2.5 mg/kg over 1 hour. Adapted from Benotti et al.[1]

Please see last page for important product information concerning contraindications, adverse reactions, patient selection, and precautionary recommendations.

*Interview on file, Winthrop Pharmaceuticals

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State-of-the-heart

Inocor® I.V.
(AMRINONE)

Dual-acting therapy,
instead of catecholamines

State-of-the-heart therapy.

(Brief Summary—see next page)

INOCOR I.V.

Two-in-one dual inotropic and vasodilator action provides improved therapy for the patient with acute heart failure.

■ Unlike catecholamines, INOCOR does not increase MVO_2 and can be used in ischemic patients with heart failure.

■ Unlike catecholamines, INOCOR does not significantly increase risk of arrhythmias (see Precautions).

Please consult full product information before prescribing. A summary follows.

INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS *General:* INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

LABORATORY TESTS *Fluid and electrolytes:* Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol; hydralazine, prazosin, isosorbide dinitrate, nitroglycerine; chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium supplements, insulin, diazepam.

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace® disopyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use in acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established.

USE IN PREGNANCY *Pregnancy category C.* In New Zealand white rabbits, amrinone has been shown to produce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amrinone intravenously at the maximum dose used, 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

ADVERSE REACTIONS *Thrombocytopenia:* Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm^3 in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case); myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution to amrinone is not certain, but possible hypersensitivity reactions should be considered in any patient maintained for a prolonged period on amrinone.

General: Additional adverse reactions observed in intravenous amrinone clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site of injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotension because of its vasodilator effect. If this occurs, amrinone administration should be reduced or discontinued. No specific antidote is known, but general measures for circulatory support should be taken.

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductions:* Asymptomatic platelet count reduction (to less than 150,000/mm^3) may be reversed within one week of a decrease in drug dosage. Further, with no change in drug dosage, the count may stabilize at lower than predrug levels without any clinical sequelae. Predrug platelet counts and frequent platelet counts during therapy are recommended to assist in decisions regarding dosage modifications.

Should a platelet count less than 150,000/mm^3 occur, the following actions may be considered:

- Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds the potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were seen infrequently with IV therapy, should severe or debilitating ones occur, the physician may wish to reduce dosage or discontinue the drug based on the usual benefit-to-risk considerations.

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Dynamics of Early and Late Left Ventricular Filling Determined by Doppler Two-Dimensional Echocardiography During Percutaneous Transluminal Coronary Angioplasty

LEIGH K. BOWMAN, MBBS, FRACP, MICHAEL W. CLEMAN, MD, HENRY S. CABIN, MD, BARRY L. ZARET, MD, and C. CARL JAFFE, MD

To study the influence of ischemia on both early and late left ventricular filling, Doppler 2-dimensional echocardiography was used to measure filling parameters during percutaneous transluminal coronary angioplasty (PTCA) in 26 patients. Doppler recordings were taken immediately before balloon inflation and continuously during balloon inflation and deflation until 60 seconds into the recovery period. During PTCA of the left anterior descending artery (16 patients) there was a 35% decrease in early peak filling rate from 269 ± 88 to 169 ± 55 ml/s ($p < 0.0005$) by 60 seconds of balloon inflation. In patients undergoing PTCA of the left circumflex (4 patients) or dominant right coronary artery (6 patients), the early peak filling rate decreased 15% from 325 ± 126 to 284 ± 137 ml/s ($p < 0.005$). The decrease in early peak filling rate became evident at approximately 15 seconds after balloon inflation and fully recovered 20 seconds after balloon deflation. Rather than an expected increase in atrial stroke volume and a decrease in early to late filling ratio during coronary occlusion, there was a 28% decrease in atrial stroke volume during left anterior descending coronary artery PTCA and a 6% decrease during right coronary and circumflex PTCA. Because of the simultaneous decrease in both early and late ventricular filling, peak early to late filling ratio was only slightly altered during PTCA. There was an 83% increase in mean pulmonary artery wedge pressure during balloon inflation from 12 ± 5 to 20 ± 4 mm Hg. In 11 of these patients global systolic function was measured on subsequent inflations during PTCA using 2-dimensional echocardiography. Ejection fraction during left anterior descending PTCA decreased from 62 ± 6 to 35 ± 7% ($p < 0.0005$) and correlated highly with the mean percent decrease in early peak filling rate ($r = 0.95$). During acute ischemia there are marked abnormalities in both early and late left ventricular filling that are paralleled by a commensurate decrease in systolic function. There is also a decrease in atrial stroke volume during coronary occlusion that may be due to atrial pump failure induced by atrial afterload mismatch.

(Am J Cardiol 1988;61:541–545)

Doppler echocardiographically derived early to late filling ratio and early peak filling rate[1,2] have been used to measure left ventricular diastolic function in patients in the resting state. Few clinical investigations have measured Doppler echocardiographically derived filling parameters during rapid fluctuations in hemodynamic variables or have assessed the influence of altered loading conditions on the atrial contribution to LV filling. Percutaneous transluminal coronary angioplasty (PTCA) provides a unique opportunity to use 2-dimensional Doppler echocardiography to study the magnitude and time course of changes in early and late left ventricular (LV) filling during dynamically changing conditions of diastolic function.[3–7] We measured Doppler-derived early and late filling rates during ischemia induced by balloon inflation during PTCA and assessed the relation of these changes to systolic dysfunction and mean pulmonary artery wedge pressure during ischemia.

From the Departments of Medicine (Cardiology) and Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut. Manuscript received September 21, 1987; revised manuscript received and accepted November 9, 1987.

Address for reprints: C. Carl Jaffe, MD, Department of Diagnostic Radiology, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510.

Methods

Patients: Twenty-six consecutive patients undergoing PTCA with normal regional wall motion in the area supplied by the artery were studied. Three patients had a history of prior infarction and regional wall motion abnormalities in areas remote to the artery undergoing PTCA (2 patients undergoing left anterior descending PTCA had inferior hypokinesis and 1 patient undergoing right coronary artery PTCA had anteroapical akinesis). The left anterior descending artery was dilated in 16 patients, the circumflex artery in 4 and dominant right coronary artery in 6. To study the influence of occlusion of different coronary beds, patients were prospectively divided into 2 groups: group I consisted of all patients undergoing left anterior descending artery PTCA and group II consisted of patients undergoing PTCA of the circumflex or right coronary artery. No patient had angiographically visible collaterals to the artery undergoing dilation. There were 22 men and 4 women, mean age 53 ± 9 years (range 44 to 70). Medications taken by the patients consisted of combined β blockers and calcium antagonists in 12 patients, calcium antagonists alone in 6 and β blockers alone in 3. Medications were not terminated before the procedure. Nitroglycerin and atropine were given to all patients when the procedure began. Informed consent using an institutionally approved form was obtained from all patients.

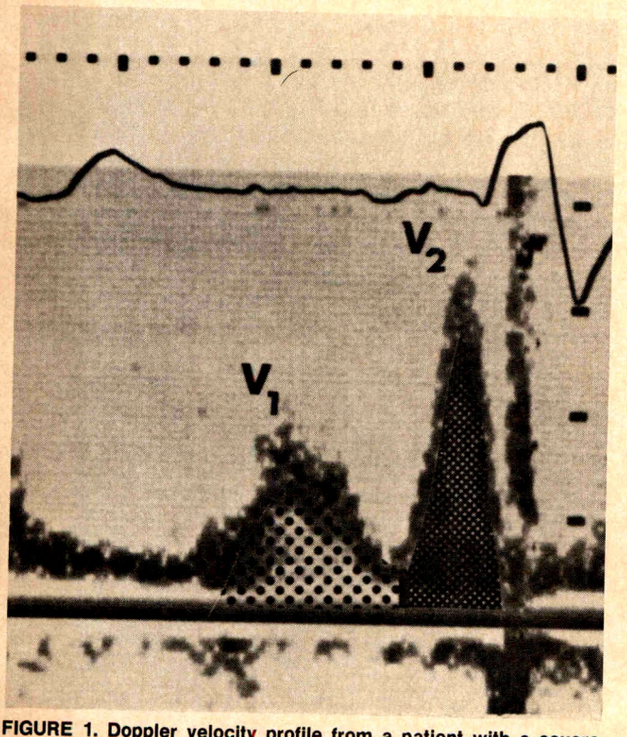

FIGURE 1. Doppler velocity profile from a patient with a severe proximal left anterior descending artery lesion and reduced early peak filling rate. V_1 = early peak filling velocity; V_2 = late peak filling velocity. The *dotted area* indicates the early filling integral and the *shaded area* indicates the late filling integral.

Angioplasty procedure: The PTCA was performed with USCI balloon dilatation catheter systems ranging in balloon diameter from 2.5 to 3.5 mm. The balloon inflation times were 60 seconds for all measured inflations. Multiple inflations were performed on each patient with balloon inflation pressures ranging from 6 to 11 atmospheres. At least 2 minutes was allowed between each inflation and return to baseline conditions was verified by examining the 2-dimensional and Doppler signals.

Doppler technique: A Hewlett Packard ultrasound machine (model 77020A) equipped with a 2.5-MHz pulsed Doppler transducer was used for the measurement of transmitral blood flow velocity. An apical 4-chamber view was obtained with the patient lying supine. The diameter of the mitral anulus was measured at the insertion of the anterior and posterior mitral leaflets as previously described.[8] The cross-sectional area of the mitral anulus was calculated assuming a circular shape. A sample volume (length 5 mm) was positioned just on the ventricular side of the mitral anulus and aligned so that the angle between the ultrasound beam and the blood flow vector was as close to zero as possible. Transmitral velocity waveform was recorded at 100 mm/s on half-inch VHS video tape. When the balloon inflation sequences were begun, ultrasonic recordings were obtained continuously from 30 seconds before inflation until 60 seconds after balloon deflation. The video tape record of the Doppler velocity profiles was analyzed by an off-line computer system. Five cardiac cycles were averaged immediately before balloon inflation. During balloon inflation, mitral inflow velocity profiles from individual cardiac cycles were observed continuously and quantitatively analyzed at the 60-second balloon inflation point. After verifying mitral anulus diameter constancy in the 11 of 26 patients in whom systolic function was assessed, mitral inflow profiles were analyzed assuming a fixed mitral anular cross-sectional area during balloon inflation.

Calculation of filling parameters: Early peak filling velocity was identified as the maximal deflection in the velocity profile before the onset of atrial contraction (Figure 1). Late peak filling velocity was defined as the maximum deflection after diastasis occurring in the second half of diastole. Early peak velocity was multiplied by the mitral anular cross-sectional area to derive early peak filling rate. The total area under the mitral inflow velocity curve was planimetered by following the most intense portion of the velocity curve to derive the time velocity integral of mitral inflow (cm), which was multipled by mitral anular cross-sectional area to derive stroke volume (in ml). The integral of the early phase of mitral filling (E integral) was defined as the area under the curve from the onset of filling until the onset of atrial flow velocity. The integral of late filling (A integral) was defined as the area under the curve from the onset of atrial flow velocity until the cessation of flow. The ratio of early peak filling velocity and late peak filling velocity was derived by dividing early peak velocity by the late peak filling velocity. The ratio of early and late filling

TABLE I Filling Parameters for Patients Undergoing Left Anterior Descending Coronary Artery Angioplasty (Group I)

	Baseline	60 Seconds	Recovery
EPFR (ml/s)	269 ± 88	169 ± 55*	275 ± 99
E integral (cm)	5.1 ± 1.5	2.9 ± 1.1*	4.9 ± 1.6
A integral (cm)	5.1 ± 1.4	3.5 ± 1.3*	4.7 ± 1.5
E/A integral	1.09 ± 0.4	1.05 ± 0.8	1.17 ± 0.6
E/A peak	0.73 ± 0.2	0.62 ± 0.3	0.77 ± 0.3

* $p < 0.001$ compared with baseline.
A integral = late filling integral; E/A = early-to-late filling ratio; E integral = early filling integral; EPFR = early peak filling rate.

TABLE II Filling Parameters for Patients Undergoing Right Coronary Artery and Left Circumflex Percutaneous Transluminal Coronary Angioplasty (Group II)

	Baseline	60 Seconds	Recovery
EPFR (ml/s)	325 ± 126	284 ± 137*	332 ± 114
E integral (cm)	6.4 ± 1.8	5.6 ± 2.2†	6.5 ± 2.0
A integral (cm)	3.8 ± 1.2	3.5 ± 0.9	3.5 ± 1.0
E/A integral	1.92 ± 1.0	1.71 ± 0.9†	2.04 ± 0.8
E/A peak	1.05 ± 0.4	0.98 ± 0.4	1.07 ± 0.4

* $p < 0.001$ compared with baseline; † $p < 0.05$ compared with baseline.
Abbreviations as in Table I.

integrals was derived by dividing the early filling integral by the late filling integral.

Measurement of systolic function: In 11 patients within this same cohort, LV systolic function was assessed by 2-dimensional echocardiography on subsequent balloon inflations in the PTCA sequence for comparison with diastolic function—in 8 patients during left anterior descending artery PTCA, in 2 during circumflex PTCA and in 1 patient during right coronary artery PTCA. Previous studies from this institution have demonstrated complete recovery of systolic function after each balloon inflation thereby permitting comparison between systolic and diastolic function on consecutive inflations.[9,10] Systolic function could not be measured in the remaining patients due to some combination of the following factors: insufficient balloon inflations, fluoroscopy during inflations, concern regarding patient stability or difficulty in obtaining adequate 2-dimensional images without undue delay. An apical long-axis view of the left ventricle, in a plane selected to give the best view of the ischemic segment, was obtained. Recordings on half-inch VHS videotape were made from 30 seconds before balloon inflation until 60 seconds after balloon deflation and analyzed using an off-line computer system. End-systolic volume, end-diastolic volume and ejection fraction were calculated from digitized endocardial contours using an area length formula.[11,12]

Pulmonary artery wedge measurements during angioplasty: To assess the relation between mean pulmonary artery wedge pressure and ventricular filling dynamics, mean pulmonary artery wedge pressure measurements were taken at baseline and during 9 balloon inflations in 9 patients (left anterior descending artery in 7, right coronary artery PTCA in 2) via a 7Fr flow-directed pulmonary artery catheter. In 4 of these patients Doppler and wedge pressures were obtained simultaneously.

Statistics: Paired and unpaired Student's *t* tests were used to assess significant differences between groups. Mean and standard deviation of data groups are reported. Linear regression using a least squares method was used to assess comparisons between data groups.

Results

Hemodynamics: Baseline heart rate was 74 ± 10 beats/min and was 75 ± 11 (difference not significant) during balloon inflation. Heart rate after 60 seconds of recovery was 73 ± 11 beats/min. Mean baseline blood pressure was 128 ± 17/77 ± 12 and decreased to 118 ± 14/68 ± 9 mm Hg after the final balloon inflation. The mean number of balloon inflations performed per patient was 6.5 ± 4.0. The mean percent stenosis decreased from 92 ± 5 to 13 ± 10% and the mean gradient across the lesion decreased from 51 ± 10 to 10 ± 6 mm Hg. The mean number of inflations before recording of the ultrasonic data 1.6 ± 1.7. The mean mitral anulus diameter in the 11 patients who had 2-dimensional studies during PTCA was 2.77 ± 0.33 at baseline and 2.79 ± 0.29 cm after 60 seconds of balloon inflation (difference not significant).

Comparison of filling rates in group I and group II: *Early filling during angioplasty:* The effect of PTCA on filling dynamics is summarized in Tables I and II. In both groups there was a decrease in early peak filling rate and E integral that occurred 15 to 20 seconds after balloon inflation and continued to decrease until balloon deflation. In the left anterior descending coronary artery patients there was a 35% decrease in early peak filling rate from 269 ± 88 to 169 ± 55 ml/s ($p < 0.0005$) and a 44% decrease in E integral from 5.1 ± 1.5 to 2.9 ± 1.1 cm. In the group II patients there was only a 13% decrease in early filling from 6.5 ± 1.8 to 5.6 ± 2.2 cm. The magnitude of the decrease in early peak filling rate during balloon inflation was significantly higher in group I than in group II patients ($p < 0.001$). In both groups there was complete recovery of early peak and integral filling. Group I patients sustained a mean decrease in stroke volume of 36% from preinflation values compared with group II patients, who sustained a 14% decrease in stroke volume.

Atrial stroke volume during angioplasty: In both groups there was a decrease in the mean atrial contribution to LV filling during balloon inflation. This decrease was much more marked in the left anterior descending coronary artery group of patients who sustained a 28% decrease in late filling integral compared with a 6% decrease in group II patients. The decrease in the atrial contribution to ventricular filling in the left anterior descending coronary artery group of patients was associated with a concomitant decrease in early filling integral and early peak filling rate. Therefore, a relatively small change in peak and integral early to late filling ratios was observed during balloon inflation.

Mean pulmonary artery wedge pressure during angioplasty: The dynamic fluctuations in ventricular filling were associated with marked changes in pulmonary artery wedge pressure. In the 9 patients mean pulmonary artery wedge increased 83% from 12 ± 5 to 20 ± 4 mm Hg during balloon inflation. This was associated with a decrease in late filling from 31 ± 9 to 20 ± 8 ml. As demonstrated in 4 of the patients (Figure 2), late filling decreased during balloon inflation as mean pulmonary artery wedge pressure increased beyond 15 mm Hg.

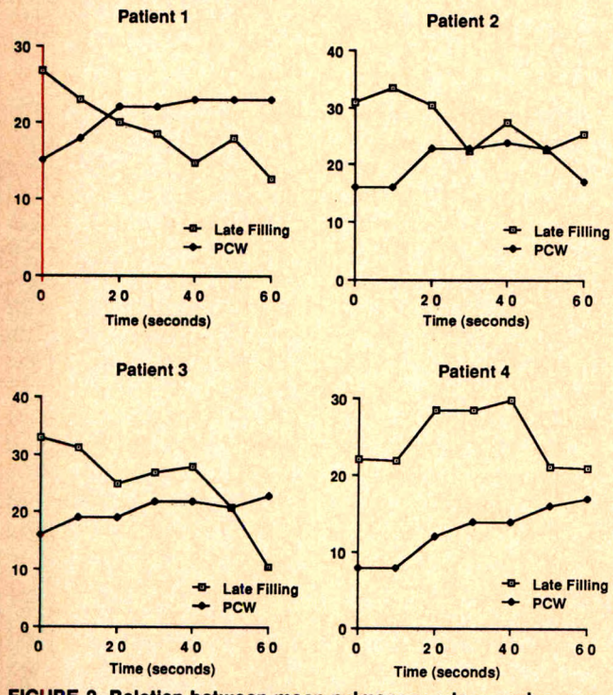

FIGURE 2. Relation between mean pulmonary artery wedge pressure (PCW) and late filling during angioplasty in 4 patients. The y axis units represent both mm Hg for mean pulmonary artery wedge pressure and ml for late filling. During balloon inflation, there is a marked decrease in late filling as pulmonary artery wedge pressure increases beyond 15 mm Hg.

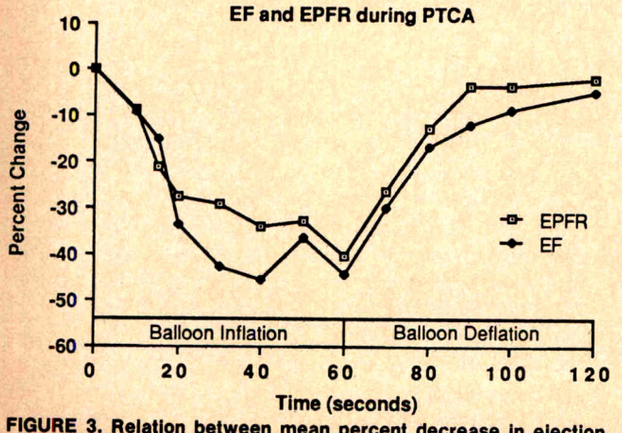

FIGURE 3. Relation between mean percent decrease in ejection fraction (EF) and mean early peak filling rate (EPFR) during balloon inflation in 11 patients undergoing left anterior descending artery angioplasty.

Relation between systolic function and early peak filling rate during angioplasty: There was a close relation between changes in systolic function and early LV filling during PTCA in both timing and magnitude. In the left anterior descending artery patients there was a decrease in mean ejection fraction from 62 ± 6 before inflation to 35 ± 6% at 60 seconds of inflation time ($p < 0.0005$) with recovery to 56 ± 8% at 30 seconds of recovery time (difference not significant compared with preinflation ejection fraction). In the 2 circumflex patients and 1 right coronary artery patient there was no significant change in ejection fraction from preinflation (66 ± 9%) to 60 seconds of inflation time (67 ± 8%). The time course and magnitude of percent change in ejection fraction compared with percent change in early peak filling rate is shown in Figure 3. In the left anterior descending artery group there was a near doubling of end systolic volume from 50 ± 20 immediately before inflation to 96 ± 34 ml at 60 seconds of inflation time ($p < 0.0001$) and a 21% increase in end-diastolic volume from 125 ± 46 to 148 ± 47 ml ($p < 0.05$). Recovery end-diastolic volume was 138 ± 40 ml (difference not significant compared with baseline).

Discussion

Previous studies[3,6,7,13] have induced ischemia by rapid atrial pacing and have measured ventriculographically derived pressure-volume curves and peak filling rates during PTCA. These investigations have demonstrated marked abnormalities of diastolic function during and after ischemia that may be caused by many factors, including increased regional myocardial stiffness,[3-5] delayed nonuniform relaxation[13-19] and alterations in right ventricular load.[16] In this study we demonstrated that Doppler-derived peak filling rate can detect marked changes in early peak filling occurring during ischemia. The baseline early peak filling rates in both groups are below the previously reported normal range of 503 ± 171 ml/s.[20] These data are consistent with previous reports of abnormal LV filling dynamics in patients with coronary artery disease.[21-22] During balloon inflation there were profound changes in LV filling dynamics. Early filling decreased within 15 to 20 seconds after the onset of balloon occlusion and completely recovered to baseline levels 20 seconds after balloon deflation. There was a mean decrease of 38% in early peak filling rate in the left anterior descending artery group but a decrease of only 14% in group II patients. This suggests that changes in early peak filling rate in the setting of acute ischemia are proportional to the amount of myocardium rendered ischemic. In association with the decrease in early filling rate during PTCA there was a concomitant decrease in global systolic function. In agreement with other studies,[23] we found that the onset of diastolic dysfunction during PTCA often preceded other measures of ischemia such as systolic function.

Late filling during angioplasty: We have demonstrated that late ventricular filling decreases during coronary occlusion particularly of the left anterior descending coronary artery. This decrease occurred at a time when there was also a marked decrease in early peak filling rate and thus the early to late filling ratio showed small change. One would have expected the early to late filling ratio to decrease during ischemia of the left ventricle as end-diastolic pressure increased and early peak filling rate decreased. This decrease in late ventricular filling during ischemia suggests that there is a limit to the compensatory increase in the atrial contribution to LV filling after increases in ventricular diastolic stiffness. This phenomenon may be explained by several factors. Severe ischemia causes both an increase in end diastolic volume[24] (20% in this study) and an upward shift in the pressure volume curve.[4] Both of these factors lead to marked increases in end-diastolic pressure and increased impedance to left atrial ejection. The thin walled atrium in the acute setting is presumably unable to eject as efficiently against this increased impedance, resulting in atrial afterload mismatch and atrial pump failure. Other studies provide supporting evidence for this concept. These dynamic fluctuations in late ventricular filling suggest that patients with severe abnormalities of diastolic function may develop atrial failure induced by high impedance to atrial ejection. This may explain preliminary reports demonstrating poor correlation between early to late filling ratios and invasive indexes of diastolic function.

Study limitations: The changes in diastolic function during PTCA noted in this study may not be fully applicable to changes seen in the setting of increased demand ischemia. Paulus et al[25] studied the differences between increased demand-induced ischemia and decreased supply-induced ischemia in dogs and found that pacing-induced ischemia induces an upward shift in the pressure volume relation as opposed to occlusive ischemia, which was associated with a downward shift in the diastolic pressure volume relation.

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Early and Late Assessment of Stenosis Geometry After Coronary Arterial Stenting

JACQUES PUEL, MD, YVES JUILLIERE, MD, MICHEL E. BERTRAND, MD, ANTHONY F. RICKARDS, MD, ULRICH SIGWART, MD, and PATRICK W. SERRUYS, MD

Early and late modifications of stenosis geometry after stenting of coronary arteries were assessed. Morphologic changes were evaluated by quantitative coronary angiography (automated edge-detection) and theoretical pressure drop across the dilated and stented stenosis was calculated from the Poiseuille formula, with turbulent resistances assuming a coronary blood flow of 1 or 3 ml/s. Eleven patients (ages 41 to 69 years, mean 55) were studied before and after angioplasty, and immediately after stent implantation. The stented coronary artery was the left anterior descending artery in 9 patients and the left circumflex in 2. Following stent implantation, an additional increase in minimal luminal cross-sectional area of the dilated vessel was observed, suggesting that the self-expanding stainless-steel endoprosthesis used had a dilating function in addition to its stenting role. Repeat angiography in 6 patients 3 months after stent implantation showed a decrease in the minimal luminal cross-sectional area without a significant change in theoretic pressure decrease. This slight reduction in vessel caliber had no hemodynamically significant repercussions. Thus, stenting of coronary arteries following dilatation is a potentially valuable technique for preventing both abrupt closure and late reduction in lumen diameter.

(Am J Cardiol 1988;61:546–553)

Although other techniques—pharmacologic,[1] mechanical and thermal[2,3]—are currently under investigation, intravascular stenting of the dilated vessels has been proposed as an alternative approach for preventing late restenosis after percutaneous transluminal coronary angioplasty (PTCA). Different prostheses have been developed and tested in animal experiments[4–10] and, recently, intravascular stents have been implanted in patients.[11] The endoprosthesis used in this open clinical trial consists of a self-expanding stainless-steel mesh that exerts a radial force on the vascular wall. So far, there are no quantitative angiographic data indicating whether the endoluminal prosthesis affects the immediate anatomic result of PTCA. On the other hand, because animal experiments have shown a neointimal proliferation totally encasing stent wires within a few weeks,[8–10] it is crucial to demonstrate that the stenotic geometry of the human stented artery does not deteriorate at short-term follow-up.

This study assesses early and delayed modifications in stenotic geometry by quantitative coronary angiography after stenting of coronary arteries in 11 patients.

Study population: The 11 patients ranged in age from 41 to 69 years (mean 55) and 8 were men. They were treated and investigated in the 3 following centers: Department of Clinical and Experimental Cardiology, CHRU Rangueil, Toulouse, France (patients 6 - 11), Catheterization Laboratory, Thoraxcenter, Rotterdam, The Netherlands (patients 1-3) and Department of Cardiology, Hospital Cardiologique, Lille, France (patients 4-5). Informed consent was obtained from each patient before the intervention. The endoprosthesis used in this study was provided by Medinvent SA. The dilated and stented coronary artery was the left anterior descending artery in 9 patients and the left circumflex artery in 2. This series of 11 patients includ-

From the Department of Clinical and Experimental Cardiology, CHRU, Rangueil, Toulouse, France; Catheterization Laboratory and Laboratory for Clinical and Experimental Image Processing, Thoraxcenter, Rotterdam, The Netherlands; Department of Cardiology, Hôpital Cardiologique, Lille, France; Department of Clinical Measurement, National Heart Institute, London, United Kingdom; and Division of Cardiology, Department of Medicine, Centre Hospitalier Universitaire de Vaudois, Lausanne, Switzerland. Manuscript received July 9, 1987; revised manuscript received and accepted October 27, 1987.

Address for reprints: Patrick W. Serruys, MD, PhD, Catheterization Laboratory and Laboratory for Clinical and Experimental Image Processing, Thoraxcenter, Erasmus University, P. O. Box 1738, 3000 DR Rotterdam, The Netherlands.

TABLE I Morphologic Results Immediately After Stenting and Three Months Later

Pt	Extent Obstruction (mm)	Obstruction Diameter (mm)	Minimal Cross-Sectional Area (mm^2)	Diameter of Stenosis (%)	Area of Stenosis (%)	Reference Diameter (mm)	Reference Area (mm^2)
1 Pre-P	7.1	0.4	0.1	82	96	2.6	5.6
Post-P	6.1	1.8	2.6	34	56	2.7	5.8
Post-S	5.3	2.0	3.2	27	46	2.8	6.1
2 Pre-P	8.2	0.7	0.4	75	94	2.8	6.0
Post-P	4.5	2.2	3.7	23	40	2.8	6.2
Post-S	5.4	2.3	4.3	22	39	3.0	7.2
3 Pre-P	6.2	1.1	0.9	56	81	2.4	4.7
Post-P	3.6	1.6	2.0	37	61	2.5	5.2
Post-S	3.8	2.5	5.0	10	19	2.8	6.3
4 Pre-P	5.5	0.7	0.4	73	93	2.5	5.0
Post-P	5.1	1.5	1.8	41	66	2.6	5.3
Post-S	4.9	2.2	3.7	17	32	2.6	5.4
5 Pre-P	6.9	1.1	1.1	61	83	2.8	6.3
Post-P	6.4	1.7	2.3	35	57	2.6	5.5
Post-S	6.3	1.6	2.1	40	64	2.7	5.9
6 Pre-P	6.2	0.9	0.7	67	88	3.0	6.9
Post-P	5.2	2.1	3.5	21	37	2.6	5.5
Post-S	6.2	2.4	4.5	13	24	2.8	6.0
3 Mths	8.6	1.9	2.9	30	51	2.7	6.1
7 Pre-P	8.1	1.6	2.0	49	74	3.1	7.7
Post-P	6.1	1.9	2.8	24	42	2.5	4.9
Post-S	7.0	2.8	6.2	13	24	3.2	8.2
3 Mths	8.5	2.3	4.4	26	44	3.1	7.8
8 Pre-P	8.6	1.5	1.8	45	70	2.8	6.2
Post-P	10.0	1.8	2.7	38	61	3.0	7.0
Post-S	9.4	2.3	4.3	23	40	3.0	7.3
3 Mths	10.8	2.3	4.4	25	43	3.1	7.8
9 Pre-P	10.0	1.6	1.9	54	79	3.4	9.3
Post-P	10.2	1.7	2.3	44	69	3.0	7.3
Post-S	8.7	2.0	3.3	39	62	3.4	8.9
3 Mths	10.3	1.8	2.7	46	70	3.4	8.9
10 Pre-P	5.6	0.8	0.5	68	89	2.6	5.3
Post-P	4.9	1.7	2.6	31	52	2.5	5.1
Post-S	7.2	2.7	6.0	15	28	3.3	8.8
3 Mths	6.3	1.9	3.0	37	61	3.1	7.8
11 Pre-P	7.6	2.0	3.1	44	69	3.6	10.1
Post-P	8.9	2.1	3.4	36	59	3.2	8.2
Post-S	7.5	2.4	4.9	33	55	3.5	9.9
3 Mths	10.9	2.0	3.2	42	65	3.5	9.4
Mean Pre-P (11)	7.3 ± 0.4	1.1 ± 0.1	1.2 ± 0.3	61 ± 4	83 ± 3	2.9 ± 0.1	6.6 ± 0.5
±SE Post-P (11)	6.4 ± 0.7	1.8 ± 0.1	2.7 ± 0.2	33 ± 2	54 ± 3	2.7 ± 0.1	6.0 ± 0.3
Post-S (11)	6.5 ± 0.5	2.3 ± 0.1	4.3 ± 0.4	23 ± 3	39 ± 5	3.0 ± 0.1	7.3 ± 0.4
Post-S (6)	7.7 ± 0.5	2.4 ± 0.1	4.9 ± 0.4	23 ± 4	39 ± 7	3.2 ± 0.1	8.2 ± 0.5
3 Mths (6)	9.2 ± 0.7	2.0 ± 0.1	3.4 ± 0.3	34 ± 3	56 ± 5	3.1 ± 0.1	8.0 ± 0.5

□ = not significant; ● = $p < 0.05$; ○ = $p < 0.01$; ■ = $p < 0.005$.
Mths = months; P = PTCA; S = stent; SE = standard error.

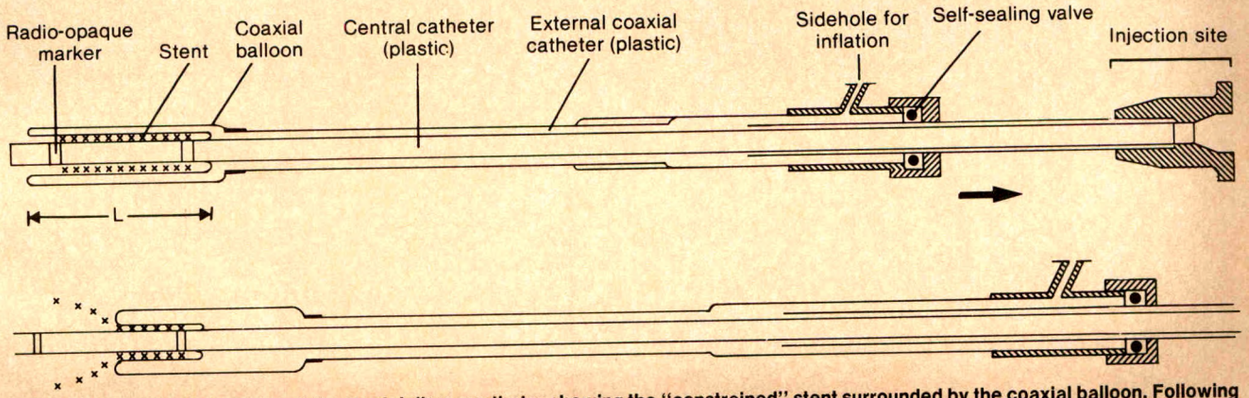

FIGURE 1. Longitudinal section of the stent delivery catheter showing the "constrained" stent surrounded by the coaxial balloon. Following inflation of the balloon, the outer sheath of the coaxial system is retracted (*arrow*) to allow the stent to expand within the arterial lumen.

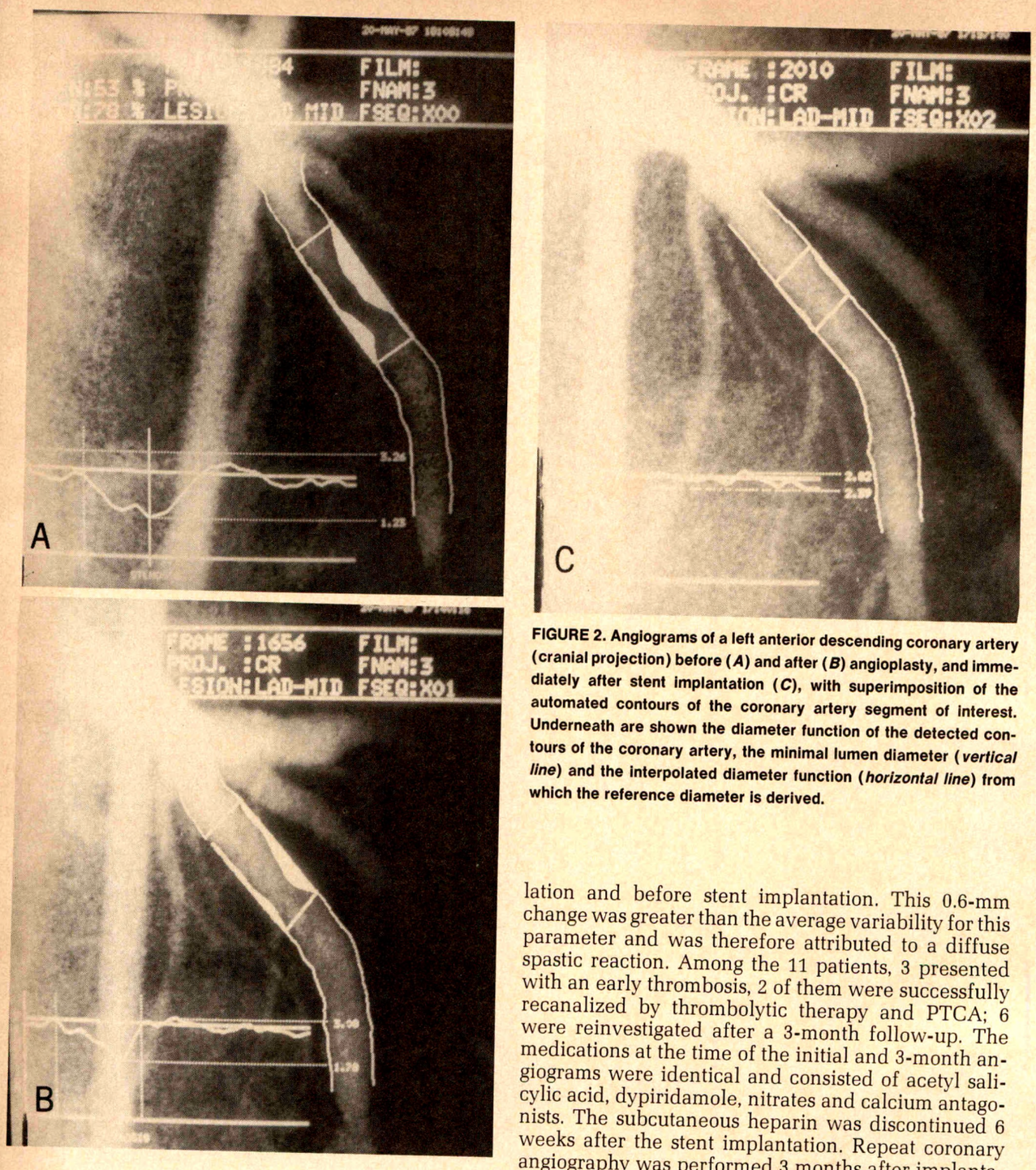

FIGURE 2. Angiograms of a left anterior descending coronary artery (cranial projection) before (*A*) and after (*B*) angioplasty, and immediately after stent implantation (*C*), with superimposition of the automated contours of the coronary artery segment of interest. Underneath are shown the diameter function of the detected contours of the coronary artery, the minimal lumen diameter (*vertical line*) and the interpolated diameter function (*horizontal line*) from which the reference diameter is derived.

ed the first 6 consecutive patients who had an endoprosthesis implanted in Toulouse for secondary prevention of restenosis and the first 5 patients with implants for primary prevention of restenosis in the pilot phase of a multicenter trial (Coronary Artery Stent Implant Study [CASIS]). No coronary spasm occurred at the time of endoprosthesis implantation. In patient 7, a transient decrease from 3.1 to 2.5 mm in the reference diameter was observed immediately after the dilation and before stent implantation. This 0.6-mm change was greater than the average variability for this parameter and was therefore attributed to a diffuse spastic reaction. Among the 11 patients, 3 presented with an early thrombosis, 2 of them were successfully recanalized by thrombolytic therapy and PTCA; 6 were reinvestigated after a 3-month follow-up. The medications at the time of the initial and 3-month angiograms were identical and consisted of acetyl salicylic acid, dypiridamole, nitrates and calcium antagonists. The subcutaneous heparin was discontinued 6 weeks after the stent implantation. Repeat coronary angiography was performed 3 months after implantation in 6 patients (5 men, 1 woman).

Methods

Description of the stent[11]: The stent is woven from a surgical-grade stainless-steel alloy formulated according to the specifications of the International Standards Organization. The prosthesis is geometrically stable, pliable and self-expanding. Its elastic and pliable properties are such that the diameter can be substantially reduced by moderate elongation. The prosthesis can be constrained on a small-diameter delivery

catheter and, as the constraining membrane is progressively removed, the elastic device assumes its original (unconstrained) larger diameter. The constrained wire-mesh prosthesis is held at the distal end of the delivery catheter by a doubled-over membrane, the outer layer of which can be progressively withdrawn. Two radiopaque metal markers on the delivery catheter facilitate identification of the end of the prosthesis at the time of its deployment. The outer diameter of the loaded catheter system is 1.57 mm and prostheses able to expand to a diameter of 6.5 mm are mounted on this delivery device (Figure 1).

In this study, unconstrained stent diameter ranged from 3.0 to 3.5 mm. The selection of stent sizes depended upon the size of the arterial segment, taking into consideration that the stent in its unconstrained form must have a diameter 0.5 mm larger than the stented vessel. The prosthesis consisted of 16 wire filaments each 0.08-mm wide.

Quantitative coronary angiography: The determination of coronary arterial dimensions from 35-mm cinefilm was performed with the computer-based Cardiovascular Angiography Analysis System.[12-15] In essence, boundaries of the relevant coronary artery segment are detected automatically from optically magnified and video-digitized regions of interest of a selected cineframe. The absolute diameter of the stenosis (in mm) is determined using the guiding catheter as a scaling device. The detected contours of the arterial and catheter segments are corrected for pincushion distortion.[12,14] A computerized estimation of the original arterial dimension at the site of the obstruction is used to define the interpolated reference region.[12,13] The interpolated percentage area stenosis and the minimal luminal cross-sectional area (mm^2) are then calculated and averaged from, if possible, at least 2, preferably orthogonal projections. The length of the lesion is determined from the diameter function on the basis of a curvature analysis.

The variability in obstruction diameter for short- (5 min), medium- (60 min) and long-term (90 days) studies ranged from 0.22 mm for the short-term study to 0.36 mm for the long-term study.[13] In the long-term study group, the lack of significant variation in the mean difference of the minimal lumen diameters suggested that no detectable progression or regression of atherosclerotic lesions had occurred over the 90-day period. Therefore, a change greater than the total measurement variability of repeated coronary cineangiography and quantitative analysis (0.36 mm for obstruction diameter; i.e., 1 standard deviation of difference of duplicate measurements) was considered significant and indicative of restenosis.

Hemodynamic assessment: The theoretic pressure drop was calculated using the arteriogram and digital computation, according to well-known formulas described in the literature:[16-18] $Pgrad = Q \cdot (Rp + Q \cdot Rt)$ where Pgrad is the theoretic transstenotic pressure decrease (mm Hg) over the stenosis, Q the mean coronary blood flow (ml/s), Rp the Poiseuille resistance and Rt the turbulent resistance.

These resistances have been defined as follows:

$$Rp = C_1 \cdot (\text{length obstruction}) / (\text{minimal cross-sectional area})^2$$

where $C_1 = 8 \cdot \pi \cdot$ (blood viscosity) with blood viscosity = 0.03 g/cm · s.

$$Rt = C_2 (1/\text{minimal cross-sectional area} - 1/\text{normal distal area})^2$$

where C_2 = (blood density)/0.266 with blood density = 1.0 g/cm^3.

The theoretic transstenotic pressure drop was calculated for a theoretic coronary blood flow of 0.5, 1 and 3 ml/s. The Poiseuille and turbulent contributions to flow resistance were determined from stenotic geometry assessed by quantitative coronary angiography.

Statistical analysis: Comparisons between post-PTCA and post-stenting measurements and between post-stenting and 3-month follow-up measurements were carried out using the Student *t* test for paired observations.

Results

Early assessment immediately after stenting (Figure 2A-C): The 11 patients were studied and a mean of

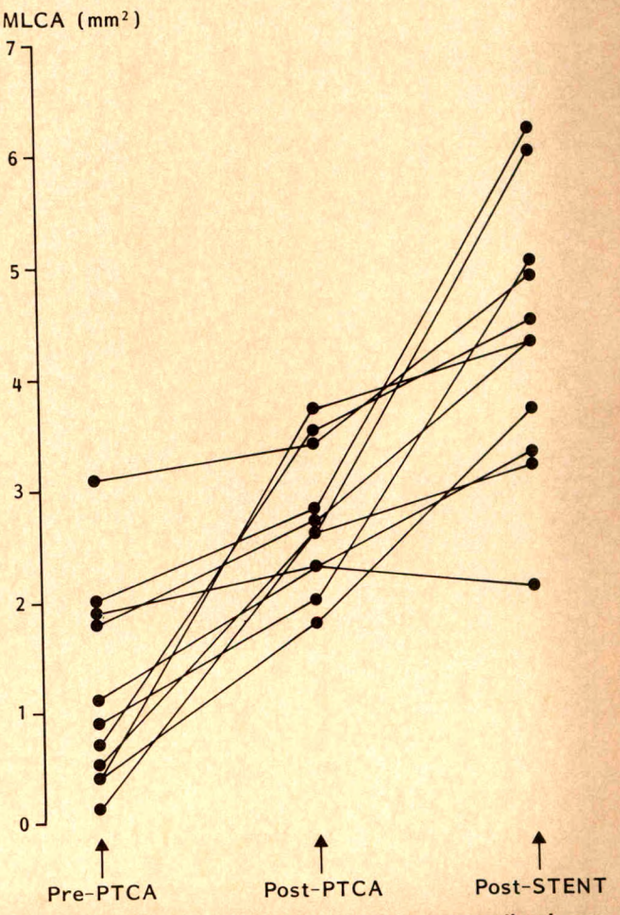

FIGURE 3. Changes in minimal luminal cross-sectional area (MLCA) between pre- (pre-PTCA) and post-angioplasty (post-PTCA), and immediately after stent implantation (post-STENT).

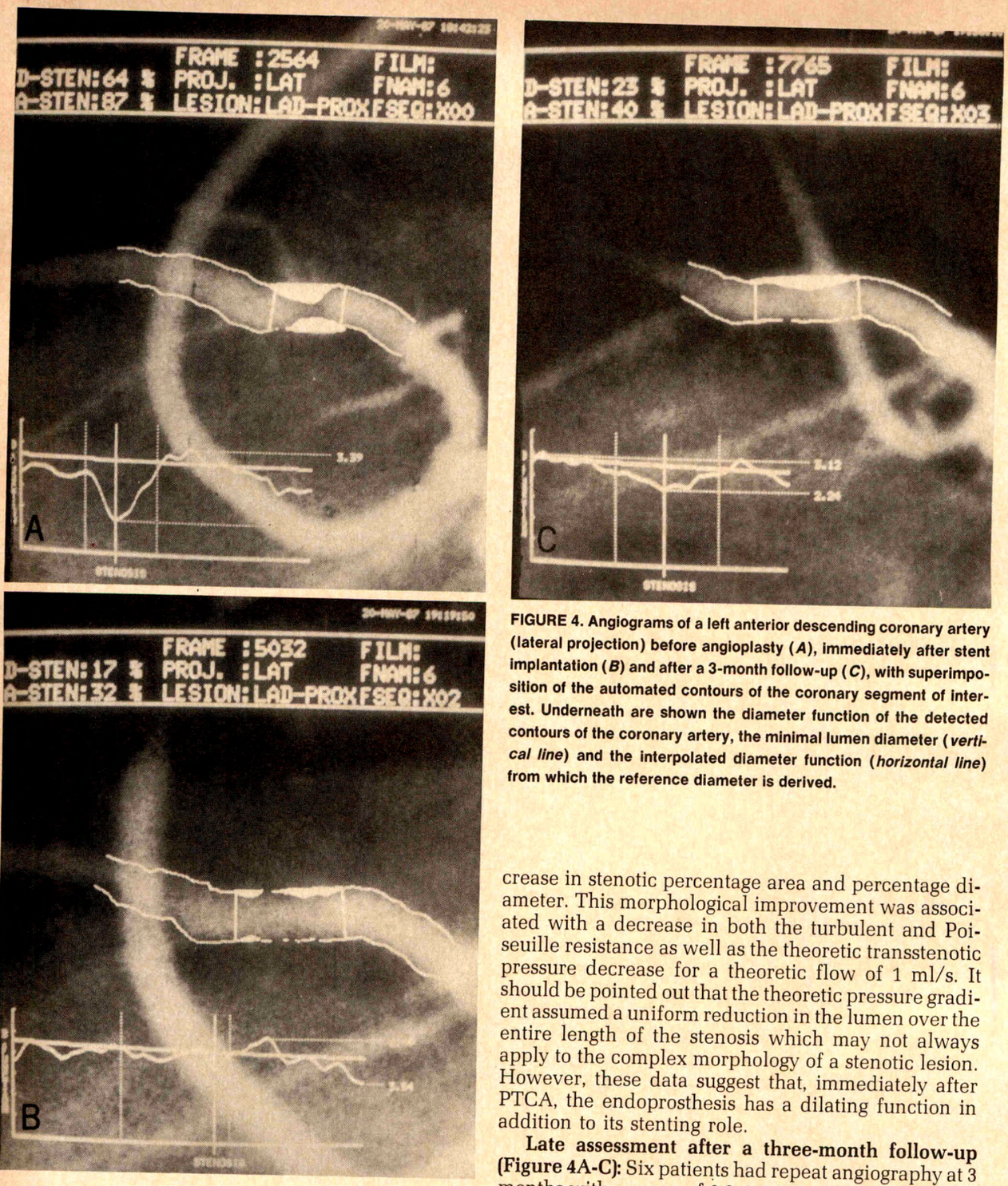

FIGURE 4. Angiograms of a left anterior descending coronary artery (lateral projection) before angioplasty (*A*), immediately after stent implantation (*B*) and after a 3-month follow-up (*C*), with superimposition of the automated contours of the coronary segment of interest. Underneath are shown the diameter function of the detected contours of the coronary artery, the minimal lumen diameter (*vertical line*) and the interpolated diameter function (*horizontal line*) from which the reference diameter is derived.

2.0 ± 0.4 angiographic projections per lesion was analyzed. The morphologic and hemodynamic data (mean ± standard error of the mean as well as the individual values of the parameters for each patient), are listed in Table I and II, respectively.

Stent implantation following PTCA resulted in an additional increase in minimal luminal cross-sectional area (Figure 3) and obstruction diameter, and a decrease in stenotic percentage area and percentage diameter. This morphological improvement was associated with a decrease in both the turbulent and Poiseuille resistance as well as the theoretic transstenotic pressure decrease for a theoretic flow of 1 ml/s. It should be pointed out that the theoretic pressure gradient assumed a uniform reduction in the lumen over the entire length of the stenosis which may not always apply to the complex morphology of a stenotic lesion. However, these data suggest that, immediately after PTCA, the endoprosthesis has a dilating function in addition to its stenting role.

Late assessment after a three-month follow-up (Figure 4A-C): Six patients had repeat angiography at 3 months with a mean of 2.0 ± 0.2 angiographic projections per lesion. The morphologic and hemodynamic data (mean ± standard error or the mean, as well as the individual values of the parameters for each patient) are listed in Table I and II, respectively.

The 3-month follow-up revealed a decrease in minimal luminal cross-sectional area (Figure 5), a decrease in obstruction diameter and an increase in stenotic percentage area and percentage diameter, when compared with the values recorded immediately after stent implantation. The obstruction diameter de-

TABLE II Hemodynamic Results Immediately After Stenting and Three Months Later

Pt	Normal Distal Area (mm^2)	Poiseuille Resistance (dynes · s · cm^{-5})	Turbulent Resistance (dynes · s · cm^{-5})	Pressure Gradient (flow = 0.5 ml/s) (mm Hg)	Pressure Gradient (flow = 1 ml/s) (mm Hg)	Pressure Gradient (flow = 3 ml/s) (mm Hg)
1 Pre-P	4.6	535	360	121*	(—)	(—)
Post-P	5.6	0.7	0.2	0.4	0.9	3.9
Post-S	4.5	0.4	0.0	0.2	0.4	1.2
2 Pre-P	4.3	39	19	24	58	(—)
Post-P	4.1	0.2	0.0	0.1	0.2	0.6
Post-S	6.0	0.2	0.0	0.1	0.2	0.6
3 Pre-P	4.3	5.8	3.3	3.7	9.1	47
Post-P	5.1	0.7	0.3	0.4	1.0	4.8
Post-S	6.6	0.1	0.0	0.0	0.1	0.3
4 Pre-P	2.7	26	17	17	43	(—)
Post-P	3.0	1.2	0.2	0.6	1.4	5.4
Post-S	4.5	0.3	0.0	0.1	0.3	0.9
5 Pre-P	5.0	4.3	1.9	2.6	6.2	30
Post-P	4.8	0.9	0.2	0.5	1.1	4.5
Post-S	5.1	1.1	0.3	0.6	1.4	6.0
6 Pre-P	6.1	13	6.0	7.8	19	92
Post-P	5.7	0.3	0.0	0.1	0.3	0.9
Post-S	5.8	0.2	0.0	0.1	0.2	0.6
3 Mths	5.9	0.8	0.1	0.4	0.9	3.3
7 Pre-P	6.4	1.5	0.4	0.8	1.9	8.1
Post-P	3.8	0.6	0.0	0.3	0.6	1.8
Post-S	6.0	0.1	0.0	0.0	0.1	0.3
3 Mths	6.5	0.3	0.0	0.1	0.3	0.9
8 Pre-P	4.6	1.9	0.4	1.0	2.2	9.1
Post-P	6.4	1.2	0.2	0.6	1.4	5.7
Post-S	6.1	0.4	0.0	0.2	0.4	1.3
3 Mths	6.6	0.4	0.0	0.2	0.4	1.4
9 Pre-P	7.7	2.8	0.6	1.5	3.4	1.4
Post-P	6.4	1.4	0.3	0.8	1.7	6.9
Post-S	6.8	0.6	0.1	0.3	0.7	2.7
3 Mths	6.1	1.1	0.2	0.6	1.3	5.1
10 Pre-P	3.8	17	11	11	28	(—)
Post-P	5.0	0.5	0.1	0.3	0.6	2.4
Post-S	8.8	0.1	0.0	0.0	0.1	0.3
3 Mths	7.4	0.5	0.1	0.3	0.6	2.4
11 Pre-P	7.4	0.6	0.1	0.3	0.7	2.7
Post-P	6.4	0.6	0.1	0.3	0.7	2.7
Post-S	8.9	0.2	0.0	0.1	0.2	0.6
3 Mths	7.4	0.8	0.1	0.4	0.9	3.3
Mean Pre-P (11)	5.2 ± 0.5	59 ± 48	38 ± 32	7 ± 2	17 ± 6	29 ± 12
±SE Post-P (11)	5.1 ± 0.3	0.8 ± 0.1	0.2 ± 0.0	0.4 ± 0.1	0.9 ± 0.1	3.6 ± 0.6
Post-S (11)	6.3 ± 0.4	0.3 ± 0.1	0.0 ± 0.0	0.1 ± 0.0	0.4 ± 0.1	1.3 ± 0.5
Post-S (6)	7.1 ± 0.6	0.3 ± 0.1	0.0 ± 0.0	0.1 ± 0.0	0.3 ± 0.1	1.0 ± 0.4
3 Mths (6)	6.6 ± 0.2	0.7 ± 0.1	0.1 ± 0.0	0.3 ± 0.1	0.7 ± 0.1	2.7 ± 0.6

* Theoretic pressure decrease calculated for a theoretic blood flow of 0.20 ml/s; (—) Theoretic pressure decrease greater than the mean aortic pressure.
□ = not significant; ● = $p < 0.05$; ○ = $p < 0.01$; ■ = $p < 0.005$.
Mths = months; P = PTCA; S = stent; SE = standard error.

creased from 2.4 ± 0.1 mm to 2.0 ± 0.1 mm and the stenotic percentage diameter increased from 23 ± 4% to 34 ± 3%. The reduction in obstruction diameter was probably due to the neointimal proliferation, which theoretically should result in a diameter reduction of 0.2 mm. The turbulent and Poiseuille resistance also increased significantly, but such an increase did not result in a hemodynamically significant pressure decrease over the stent for theoretic flow rates of 1 to 3 ml/s.

Discussion

A promising new approach to reduce the rate of restenosis is the implantation of an intravascular endoprosthesis. The principle of introducing intraarterial grafts percutaneously was first described by Dotter in 1969.[5] During the last few years, variants of the original technique using thermal-shaped memory alloys,[4-19] expanding spring steel spirals,[6] expanding stainless-steel stents[10] and expanding woven stainless-steel meshes[7-9] have been reported in animal experiments.

Recently, intravascular stents have been implanted in humans to prevent occlusion and restenosis after PTCA.[11] The endoprosthesis used in this first clinical series consisted of a new self-expandable stainless-steel mesh.[11] The early assessment immediately after stent implantation showed an additional morphologic improvement over the PTCA results, affecting both the stenotic and nonstenotic segments, which demonstrates the intrinsic dilating force of the stent. Sigwart et al[11] have indicated that this prosthesis has an elastic radial force that tends to dilate the artery when the

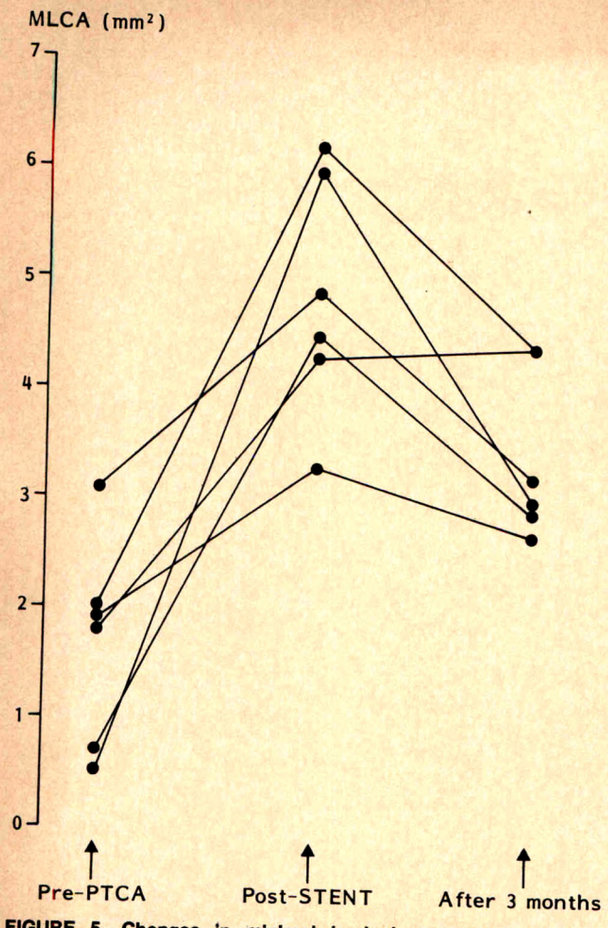

FIGURE 5. Changes in minimal luminal cross-sectional area (MLCA) between pre-angioplasty (pre-PTCA) and immediately after stent implantation (post-STENT) and after a 3-month follow-up.

vessel caliber is less than that of uncontrained stent diameter. Dilatation continues until an equilibrium is achieved between the circumferential elastic resistance of the arterial wall and the dilating force of the prosthesis. Previously, Wright et al[10] showed that the expansile pressure depends on the recipient vessel diameter and on the intrinsic dilating force of the stent itself. The present study confirms—in human beings—the dilating capacity of the stent.

In this study, changes in the nonstenotic segments are reflected in the significant increase observed in the interpolated reference diameter after stent implantation. In the interpretation of this result, 3 facts have to be considered with regard to the determination of the reference diameter.

First, the "interpolated" technique for the determination of the reference diameter incorporates in its computation all the individual diameter values of the proximal and distal coronary segments, which invariably include stented, but nonstenotic segments. Second, the stent size is selected so as to have in its unconstrained state a diameter 0.5 mm larger than the vessel in which it is to be implanted, to ensure that the device will be securely anchored. Third, as the stent has a length ranging from 15 to 22 mm, it is not surprising that the radial force exerted by the stent has a dilating effect on the nonstenotic segments included in the computation of the interpolated reference diameter.

All the long-term experimental studies have shown that in animals neointimal proliferation produces a covering of the stent's luminal surface. The time taken for the endothelialization process to cover the stent surface depends on the thickness of the wire filaments[7,8,10,11] (3 weeks for the prosthesis used in this study).[11] Neointimal thickening varies from 0.2 to 0.5 mm[9,11] and depends on the diameter of the prosthesis.[8] However, most investigators have not found important angiographic reductions in vessel diameter after stent implantation,[4,8,10,11] except for Dotter in his initial study.[5] In a previous study with conventional analysis of in vivo arteriograms, neointimal thickening was not described.[9] In contradistinction, our study demonstrates that a small diffuse narrowing of the vessel's lumen is detectable by quantitative coronary angiography. In the present study, neointimal proliferation was estimated to produce a 0.200-mm reduction in vessel diameter, corresponding to a 11 ± 3% reduction in the stenotic percentage diameter. These results are consistent with animal studies on neointimal thickening[9,11] occurring after stent implantation.

Appendix—Participating Centers and Collaborators

Department of Clinical and Experimental Cardiology, CHRU Rangueil, Toulouse, France: J.P. Bounhoure, MD, A. Courtault, MD, F. Joffre, MD, J. Puel, MD, H. Rousseau, MD.

Catheterization Laboratory and Laboratory for Clinical and Experimental Image Processing, Thoraxcenter, Rotterdam, The Netherlands: K. Beatt, MRCP, M. v.d. Brand, MD, P.J. de Feyter, MD, P.G. Hugenholtz, MD, Y. Juilliere, MD, J.H.C. Reiber, PhD, J. Roelandt, MD, P.W. Serruys, MD.

Department of Cardiology, Hôpital Cardiologique, Lille, France: M.E. Bertrand, MD, J.M. Lablanche, MD.

Department of Clinical Measurement, National Heart Institute, London, U.K.: A. F. Rickards, MD, P. Urban, MD.

Division of Cardiology, Department of Medicine, CHUV, Lausanne, Switzerland: L. Kappenberger, MD, U. Sigwart MD.

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Intraaortic Balloon Pumping for Prolonged Circulatory Support

PAUL S. FREED, MS, TARIK WASFIE, MD, BARINA ZADO, MD, and ADRIAN KANTROWITZ, MD

Prolonged circulatory support with an intraaortic balloon pump (IABP) is controversial, in part because it has not been performed frequently enough to base treatment policy on adequate data. To help clarify this problem, 733 cases of consecutive patients who were supported by IABP between 1967 and 1982 were analyzed. Twenty-seven patients were supported for 20 days or more (range 20 to 71). Twelve (44%) had prior histories of chronic congestive heart failure. Complications were more frequent in prolonged-support patients than in those assisted for <20 days (vascular, 37% vs 15%, p = 0.001; infectious, 67% vs 25%, p = 0.0001; and bleeding, 26% vs 15%, p = 0.04, respectively). The survival rate of prolonged-support patients, however, was 63% (17 of 27), essentially the same as that of the controls (57%, p = 0.5). Of 17 prolonged-pumping patients discharged alive from the hospital, 9 died within 6 months but 8 survived >2 years. Among congestive heart failure patients, none was a long-term survivor. Prolonged IABP support in congestive heart failure patients lacking surgically correctable lesions can extend life while arrangements for definitive therapy are made (transplant, permanent mechanical assistance). Where definitive therapy is unavailable, IABP may provide additional months of life.

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Although clinical efficacy of intraaortic balloon pumping (IABP) for short-term support is well documented,[1–5] little has been reported on prolonged IABP.[6–10] The present report attempts to determine the morbidity, mortality and therapeutic efficacy of prolonged IABP with data obtained in a retrospective study of a 16-year experience.

Methods

Between 1967 and 1982, 872 attempts to perform IABP were made in 733 patients, 37 of them at Maimonides Medical Center in New York and the remainder at Sinai Hospital of Detroit.[5] Details of technique, adjunctive medical management and type of equipment used have been described previously.[11–14]

Throughout our experience, we attempted to remove the intraaortic balloon pump when the patient was "hemodynamically stable" or a complication occurred which made the risk/benefit ratio excessively high, e.g., threatened loss of a limb in a patient pumped for preoperative support. Generally, if the cardiac index was >2.2 liter/min/m^2, pulmonary capillary pressure <18 mm Hg and arterial blood pressure normal, assistance was discontinued. Alternatively, the balloon drive pressure was reduced to below the patient's systolic pressure for 30 to 60 minutes, the patient observed, and the balloon removed if no trend toward hemodynamic deterioration resulted. In patients in whom circulatory decompensation developed during trial discontinuation of IABP, weaning was attempted. The drive pressure was decreased by 5 to 10 mm Hg/hour, intravascular fluid volume adjusted and digitalis, diuretics, nitrates and (since 1979) oral vasodilators administered. When the drive pressure reached a level below the patient's diastolic pressure, IABP was discontinued and the balloon removed. If the patient's hemodynamic status deteriorated during

From the Sinai Hospital of Detroit, Detroit, and Wayne State University, School of Medicine, Detroit, Michigan. This study was supported by grants from the General Research Fund of Sinai Hospital of Detroit, Michigan, and the Cardiac Surgery Research Foundation, New York, New York. Manuscript received July 1, 1987; revised manuscript received and accepted November 11, 1987.

Address for reprints: Adrian Kantrowitz, MD, Sinai Hospital of Detroit, 6767 West Outer Drive, Detroit, Michigan 48235.

TABLE I Preexisting Conditions in Patients Supported with Intraaortic Balloon Pumping

Condition	Prolonged-Support Pts (n = 27) No. (%)	Controls (n = 672) No. (%)	p Value
Diabetes mellitus	5 (19)	122 (18)	0.9
Systemic hypertension	8 (30)	233 (35)	0.6
Coronary heart disease	14 (52)	435 (65)	0.2
Myocardial infarction	14 (52)	294 (44)	0.4
Valvular heart disease	1 (4)	50 (7)	0.5
Chronic CHF	12 (44)	134 (20)	0.002

CHF = congestive heart failure.

TABLE II Indications for Intraaortic Balloon Pumping

Indications*	Prolonged-Support Pts (n = 27) No. (%)	Controls (n = 672) No. (%)	p Value
Cardiogenic shock	7 (26)	185 (28)	0.9
Chronic CHF	10 (37)	60 (9)	0.0001
Unstable angina	5 (19)	150 (22)	0.6
Myocardial infarction	4 (15)	92 (14)	0.9
Cardiomyopathy	3 (11)	7 (1)	0.0001
Mitral regurgitation	1 (4)	19 (3)	0.8
Ventricular septal defect	4 (15)	16 (2)	0.0001
Ventricular arrhythmia	1 (3)	23 (3)	0.8
Postoperative pump failure	2 (7)	35 (5)	0.6
Low output syndrome	2 (7)	31 (5)	0.5
Other†	0 (0)	220 (33)	—

* Multiple indications possible.
† Includes preoperative support, coming off cardiopulmonary bypass and catheterization support.
CHF = congestive heart failure.

weaning, full-scale IABP was resumed and weaning attempted again 6 to 24 hours later.

In 27 patients IABP was continued for 20 days or longer before weaning could be accomplished. Findings in these patients, the "prolonged-support group," were compared with those of a control group of 672 patients in whom IABP was performed for shorter periods (1 hour to 19 days). For purposes of analysis, all complications that could not be assigned with certainty to another cause were treated as due to IABP.

The statistical significance of differences between categorical variables was determined by means of chi-square analysis; continuous variables were compared by means of the 2-tailed Student's *t* test. A p value of 0.05 or less was regarded as significant.

Observations

Duration of intraaortic balloon pumping, age, sex and preexisting conditions: For the 27 patients in the prolonged-support group, the duration of assistance ranged from 20 to 71 days (average 33 days, median 34 days). The mean age of the patients was 57 years (range 33 to 77). Twenty-three were men and 4 women. In the control group, the average duration of IABP was 96 hours (median 76 hours). The mean age of the patients was 57 years (range 17 to 87); 503 were men and 169 were women.

Table I compares the distribution of preexisting conditions (originated before the present hospital admission) in the prolonged-support and control groups. The 2 groups differed significantly only in the frequency of chronic congestive heart failure (defined as impairment in cardiac function with inadequate cardiac output necessary to meet the metabolic needs of the body as manifested by signs and symptoms of systemic or pulmonary venous congestion, or both).

Indications for intraaortic balloon pumping: Table II contrasts the frequencies of indications for IABP in the 2 groups. The frequency of congestive heart failure as an indication for balloon support was 37% in the prolonged-support group and 9% in the control group; this difference was highly significant. Cardiomyopathy and ventricular septal defect also were significantly more frequent in the prolonged IABP group. Whereas there were many patients pumped prophylactically (preoperative or catheterization support) in the control group, no patients were on prophylactic IABP in the prolonged-support group. All but the 5 prolonged-support patients with unstable angina were experiencing heart failure just prior to assistance.

Cineangiocardiography: Cardiac catheterization and angiocardiography were performed in 23 of the 27 patients of the prolonged-support group (Tables III and IV). In 10, the left ventricular ejection fraction was 35% or less and in 9 the left ventricular end-diastolic pressure was 25 mm Hg or more. In 21 patients, coronary occlusion of various degree was demonstrated. Three patients had acquired ventricular septal defects; 7, mitral regurgitation; and 10, left ventricular aneurysms.

Complications: Table V compares the incidence of complications in patients who received prolonged support and those who did not. The frequencies of vascular, infectious and bleeding complications were higher in patients subjected to prolonged IABP.

Many of the complications in both groups were transient and minor. Significant complications in the prolonged-support group included 2 instances of ischemic neuropathy that required physiotherapy for residual impairment. Thromboembolism necessitated transmetatarsal amputation in 1 patient. Another had gangrene of the foot at death. Two patients died of heart failure exacerbated by septicemia.

Surgery: After or during IABP support, 12 prolonged-support patients had open-heart surgery (Tables III and IV), of whom 10 survived to leave the hospital. Two patients died, 1 of septicemia and 1 of congestive heart failure.

Survival: Of the 27 patients, 17 (63%) were discharged alive. Five patients died during IABP and 5 shortly after its termination. Eight of the 17 patients discharged alive survived longer than 2 years (patients 14–16, 18, 21, 22, 24 and 25 in Table IV). The remaining 9 died within 6 months, in all instances but 1 (patient

TABLE III Nonsurvivors with Prolonged Intraaortic Balloon Pumping

Pt	Age (yr), Sex	Previous History	Catherization Results: Coronary Arteries Narrowed >70% in Diameter	MR	VSD	LVA	LVDP (mm Hg)	EF (%)	Primary Indications for IABP	Cardiac Surgery	Duration (days)
1	34, M	CAD, MI	LM, LAD, R, AL	+++	–	–	17		CHF	—	20
2	65, M	CHF, SH	LC, R, AL	–	–	–		30	CS	—	35
3	45, M	MI, CHF	LC, LAD, R, AL	–	–	+	25	25	CHF	—	30
4	60, M	CAD, SH	LC, LAD, R, AL, PLC	–	–	+	33	30	CS	—	25
5	52, M	DM, CAD, MI							MI/unstable AP	—	21
6	58, M	CAD, MI, CHF	R	–	–	–	30	24	CHF	—	71
7	53, M	CAD, MI, CHF	LC, LAD, R, AL, PLC	–	–	–	24	35	CHF	LVAD	43
8	74, M	DM, CAD, MI, SH							Unstable AP	—	41
9	56, M	DM	LC, LAD, R	–	+	–	31		VSD	—	28
10	77, F	CHF, MI, SH							MI/VSD	CAB	24

AL = anterolateral of the LAD; AP = angina pectoris; CAB = coronary artery bypass; CAD = coronary artery disease; CHF = congestive heart failure; CS = cardiogenic shock; DM = diabetes mellitus; EF = ejection fraction; LAD = left anterior descending; LC = left circumflex; LM = left main coronary artery; LVA = left ventricular aneurysm or aneurysmectomy; LVAD = left ventricular assist device implantation; LVDP = left ventricular end diastolic pressure; MI = myocardial infarction; MR = mitral regurgitation or valve replacement; PLC = posterolateral of the LC; RCA = right coronary artery; RHD = rheumatic heart disease; SH = systemic hypertension; VSD = ventricular septal defect or repair.

TABLE IV Survivors with Prolonged Intraaortic Balloon Pumping

Pt	Age (yr), Sex	Previous History	Catherization Results: Coronary Arteries Narrowed >70% in Diameter	MR	VSD	LVA	LVDP (mm Hg)	EF (%)	Primary Indications for IABP	Cardiac Surgery	Duration (days)	Survival (months)
11	34, M	—	LAD, R	–	–	–			CS	—	34	6
12	61, M	MI, CHF	LAD, R	–	–	+	18	18	CHF	—	66	4
13	55, M	CAD, MI	LAD, R, PLC	–	–	+	23	64	Unstable AP	—	22	3
14	61, M	CAD, MI	LAD, R	–	–	+	22	35	Arrhythmia	LVA	39	30*
15	69, F	CAD, SH	LC	++++	–	–	21		Card shock/MI	MR/CAB	23	90*
16	58, F	DM, SH	LAD	–	–	+		45	CHF	LVA	39	84*
17	59, M	CHF	—	++++	–	–	32	35	CHF	—	24	3
18	44, M	MI	LAD, PLC	+	–	–	21	57	Unstable AP	CAB	26	75*
19	56, M	CHF	—	+++	–	–	32	11	Cardiomyopathy	—	33	1
20	71, M	RHD, MI, CHF	—	++++	–	–	34	15	CHF/MR	MR	25	4
21	63, M	CAD	—	–	+	+	40		CS/VSD	VSD/LVA	32	36*
22	55, M	—	LC, LAD, R	–	–	–	32		CS	CAB/LVA	27	28
23	60, M	CAD, MI, CHF	LAD	–	–	+	18		CHF	—	23	2
24	63, M	—	LAD, R	–	–	–	18	38	CS/VSD	VSD	40	105*
25	58, F	CAD, SH	LAD, R	–	–	–	16	37	Unstable AP	CAB/LVA	51	36
26	40, M	CHF							CHF	—	34	3
27	58, M	DM, SH, CAD, MI, CHF	LAD, R, AL, PLC	–	–	+	22	35	MI	CAB/LVA	23	6

Abbreviations as in Table III.
* Alive at last follow-up.

20, cerebrovascular accident) of congestive heart failure.

Discussion

Theoretic considerations would support the expectation that patients receiving prolonged IABP support are to experience more complications and shorter survival than those assisted for shorter periods of time.[15,16] This prevailing opinion discourages attempts to maintain patients on IABP support for more than a few days. However, our findings only partially confirmed this expectation. Although complication rates in the prolonged-support group were substantially higher, the survival rate was the same as that of the controls. Many of the increased complications were minor, although 2 were contributory to the patient's death.

All types of complications (vascular, infectious and bleeding) of IABP were significantly more frequent in the prolonged-support group. Although the rate of local infection did not appear to be related to the duration of IABP, the incidence of fever and bacteremia did.[5] The rate of bacteremia seemed to rise after 10 days of assistance. Although the majority of patients recovered completely (7 of 9 instances), the risk of death from septicemia superimposed on an already failing heart is obviously real.

All patients in this study, but especially those in the prolonged-support group, had multiple invasive pro-

cedures and were carefully observed for an extended time interval. Because of this, and the policy of attributing complications of doubtful origin to IABP, the frequency of infectious complications attributed to the support procedure was undoubtedly overestimated.

The percentage of prolonged-support patients surviving to hospital discharge was essentially the same as that of the controls, 63 versus 57% (p = 0.5). This finding may in part be due to the fact that the sickest patients died before 20 days of support elapsed, and thus were excluded from the prolonged-support group.

A more interesting finding was that 9 of the 17 patients discharged from the hospital died within 6 months, whereas the remaining 8 survived more than 2 years. As Table IV shows, none of the long-term survivors had a prior history of chronic congestive heart failure, but 7 of the 9 who died early did.

Thus, our study identified 2 types of patient. The first type included those who benefited temporarily from support and could be discharged from the hospital, only to succumb within 6 months, and the second included those with prolonged IABP support and concomitant corrective surgery who became long-term survivors. The 2 groups could be distinguished by a history of chronic congestive heart failure.

It must be noted that most of the prolonged-support patients were treated between 1970 and 1977. Clinical practice at that time was to delay cardiac surgery for treatment of mechanical lesions until the margin of a myocardial infarct was fibrosed (3 to 4 weeks) and the hemodynamic status of the patient stabilized. This accounts for the large percentage of surgical cases among the prolonged-support group (12 of 27). Current practice in general and at our institution is more aggressive and would have resulted in much earlier operation in most of the 12 patients.

Because this was a retrospective study and the number of prolonged-support patients was small, its findings have the standing of relevant hypotheses for investigation in a prospective study rather than of established conclusions. Nevertheless, conclusions of interest from a clinical management perspective can be proposed, including the fact that maintaining balloon-dependent patients in whom surgical correction of anatomic lesions is not possible on prolonged IABP support is feasible, although at the cost of an increased complication rate. Such practice may be justifiable when the patient has to wait for definitive treatment, such as heart transplantation, or the implantation of a mechanical heart-assist device.[17-19] In patients in whom definitive therapy cannot be performed, prolonged IABP may result in sufficient improvement in cardiac function to prolong life a few months.

TABLE V Complication Rates in Patients Supported by Intraaortic Balloon Pumping

Complication	Prolonged-Support Pts (n = 27) No. (%)	Controls (n = 672) No. (%)	p Value
Vascular*	10 (37)	100 (15)	0.001
Infectious †	18 (67)	164 (25)	0.0001
Bleeding	7 (26)	94 (15)	0.04

* Vascular complications include pain in the leg, neurologic complications, thromboemboli, aortic dissection and amputation.

† Infectious complications include fever, local wound infection and bacteremia.

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Risks Associated With Intraaortic Balloon Pumping in Patients With and Without Diabetes Mellitus

TARIK WASFIE, MD, PAUL S. FREED, MS, MELVYN RUBENFIRE, MD, WALDEMAR WAJSZCZUK, MD, PAULA REIMANN, RN, WITOLD BROZYNA, MD, M. ANTHONY SCHORK, PhD, JAY KOZLOWSKI, MD, and ADRIAN KANTROWITZ, MD

Between 1967 and 1982, intraaortic balloon pumping (IABP) was attempted in 733 patients. Of these, 132 were diabetic: 51 patients were managed with diet alone, 46 patients took oral hypoglycemic agents and 35 patients required insulin. Vascular complications associated with IABP occurred in 34% of the insulin-dependent diabetics, in 18% of other diabetics and in 14% of nondiabetic patients. Infectious complications were 37, 22 and 25%, respectively. Seventy-five diabetic patients (57%) were discharged alive from the hospital after balloon pumping, essentially the same proportion as among nondiabetic patients (58%). It is concluded that although diabetics incur a higher complication rate, IABP is not contraindicated.

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Diabetes mellitus (DM) is associated with an increased frequency of vascular occlusive disease and infections.[1–5] It is not known, however, if these sequelae place diabetic patients at heightened risk of complications due to intraaortic balloon pumping (IABP). We compared the outcome of IABP in diabetic and nondiabetic subjects in a series of 733 patients for whom this mechanical cardiac assistance was attempted.

Methods

Over almost 16 years between June 1967 and December 1982, we attempted to perform IABP in 733 patients (37 at Maimonides Medical Center in Brooklyn, New York, and 696 at Sinai Hospital of Detroit, Michigan). The details of technique—performance of balloon pumping, adjunctive medical management and equipment used—have been described previously.[6–9]

The 733 patients were subjected to 872 attempts to insert the IABP. For each insertion attempt, the patient's chart was examined by a physician to determine identifying information, the patient's age and sex, relevant prior history, the indication for balloon pumping, the dates of balloon insertion and removal, the complications of the procedure, the hospital location where the procedure was attempted, type of balloon used, causes of insertion failure, therapy given before, during and after mechanical assistance, findings at angiocardiography and the nature of any associated cardiac surgical procedure. Also recorded were the duration of balloon pumping and the patient's status at hospital discharge. Where available, autopsy findings were noted.[10]

In all, 190 variables for each insertion attempt were coded and entered into a computer for analysis. For the present study, subsets of data on diabetic and nondiabetic patients were extracted for analysis.

Percutaneous balloon insertion technique was attempted in 95 insertions (17 in diabetic patients).

Data analysis: Complications of balloon pumping were classified as follows.

Category I: Spontaneous resolution without treatment, with balloon pump in situ (e.g., loss of peripheral distal pulse, serosanguinous discharge, temperature spike). *Category II:* Resolution after treatment or removal of balloon pump (e.g., ischemia of limb, fever, bleeding from arteriotomy, infection). *Category III:* Residual deficit (e.g., foot drop, neuropathy). *Category IV:* Contributory cause of death (e.g., retroperitoneal bleeding from ruptured iliac artery, bacteremia, cardiac arrest during femoral artery embolectomy under general anesthesia).

From Sinai Hospital of Detroit, Detroit, Wayne State University, School of Medicine, Detroit, and The University of Michigan, Ann Arbor, Michigan. This study was supported by grants from The General Research Fund of Sinai Hospital of Detroit, Detroit, Michigan, and the Cardiac Surgery Research Foundation, New York, New York. Manuscript received July 1, 1987; revised manuscript received and accepted October 26, 1987.

Address for reprints: Adrian Kantrowitz, MD, Sinai Hospital of Detroit, 6767 West Outer Drive, Detroit, Michigan 48235.

For several conditions detected during or after IABP (e.g., fever, bleeding, organ emboli), it was impossible to establish a cause-effect relation between attempted or accomplished pumping and the occurrence of the complication. Therefore, unless the complication could be shown to be unrelated to IABP, it was attributed to the procedure.

Differences between categorical variables were tested for statistical significance using chi-square analysis; values for continuous variables were compared using the 2-tailed Student's *t* test. A p value ≤ 0.05 was considered significant. A multivariate risk factor analysis with a logistic regression model[11] was used to determine if any combinations of predictor variables could define subsets of patients at heightened risk of complications.

Results

Of the 733 patients, 132 had DM by history with the diagnosis confirmed during the hospitalization in which IABP was attempted. In 652 patients (89%), the first attempt to insert the IABP succeeded; 46 patients (6%) required 2 or more attempts. The IABP could not be put into place in 35 patients (5%). Thus, attempts to insert the IABP were successful in 95% of patients overall. After multiple attempts, the rate of failure to insert the IABP was no different in the diabetic and nondiabetic patients (4 vs 5%, p = 0.6).

Seventy-nine patients were men (60%), and 53 were women (40%). They ranged in age from 35 to 78 years. The median age for the group was 60 years (58 years for men and 61 years for women). Forty-one patients (31%) were managed with diet alone, 46 patients (35%) took oral hypoglycemic agents and 35 (27%) required insulin. In the remaining 10 patients, no information about the management of the diabetes was available.

In the nondiabetic group there were 468 men (77%) and 133 women (23%). Women constituted half of the insulin-dependent diabetic patients and 34% of the noninsulin-dependent diabetic patients. They ranged in age from 16 to 87 years. The median age of the nondiabetic subset was 58 years (57 for men and 62 for women).

For the purposes of analysis, the patients were regrouped into 3 sets: nondiabetic (601), diabetic, noninsulin dependent (97, including the 10 for whom management information was unavailable) and diabetic, insulin-dependent (35). For some analyses, the 2 latter sets had to be merged because of the small number of patients in certain subsets (e.g., insulin-dependent diabetics with a history of valvular heart disease).

Table I compares the distribution of relevant prior diagnoses in diabetic and nondiabetic patients. Diabetic patients had a higher rate of systemic hypertension, 48% (54% for insulin-dependent diabetics, 46% for other diabetics) than nondiabetics (32%). However, the frequencies of coronary artery disease, myocardial infarction, congestive heart failure, peripheral vascular disease, valvular heart disease and cerebrovascular accidents were essentially the same in the 2 groups.

TABLE I Distribution of Prior Diagnoses Among Diabetic and Nondiabetic Patients

	Diabetic Pts (n = 132)		Nondiabetic Pts (n = 601)		
Condition	No.	Frequency (%)	No.	Frequency (%)	p Value
AMI	60	(45)	264	(44)	0.7
CAD	91	(69)	375	(62)	0.1
CHF	34	(26)	119	(20)	0.1
CVA	8	(6)	37	(6)	0.9
PVD	11	(8)	26	(4)	0.5
SH	64	(48)	192	(32)	0.01
VHD	9	(7)	46	(8)	0.7
Total	271		1,061		
Average/Pt		2.1		1.78	0.2

AMI = acute myocardial infarction; CAD = coronary artery disease; CHF = congestive heart failure; CVA = cerebrovascular accident; PVD = peripheral vascular disease; SH = systemic hypertension; VHD = valvular heart disease.

TABLE II Distribution of Indications for Balloon Pumping in Diabetic and Nondiabetic Patients

	Diabetic Pts (n = 132)		Nondiabetic Pts (n = 601)		
Indication*	No.	Frequency (%)	No.	Frequency (%)	p Value
AMI	16	(12)	89	(15)	0.4
Arrhythmia	2	(2)	19	(3)	0.3
Catheterization support	2	(2)	7	(1)	0.7
CHF	19	(14)	53	(9)	0.05
Low CO	5	(4)	28	(5)	0.6
MR	2	(2)	22	(4)	0.2
PO pump failure	6	(5)	33	(6)	0.6
Preoperative support	29	(22)	124	(21)	0.7
Shock	35	(27)	163	(27)	0.8
Unstable angina	36	(27)	133	(22)	0.2
VSD	2	(2)	18	(3)	0.3
Weaning from oxygenator	9	(7)	58	(10)	0.3

* Some patients presented with more than 1 indication.
CO = cardiac output; MR = mitral regurgitation; PO = postoperative; VSD = ventricular septal defect; other abbreviations as in Table I.

Table II shows the frequencies of the various indications for IABP in diabetic and nondiabetic patients. Unstable angina, cardiogenic shock and preoperative support were by far the most frequent indications in both groups. The frequency of congestive heart failure as an indication was greater in diabetic (14%) than in nondiabetic patients (9%). Mitral regurgitation, arrhythmias and ventricular septal defects occurred less frequently in diabetics, but the statistical significance of this difference could not be demonstrated because of the small number of patients.

Table III compares the 3 sets of patients for the frequency and severity of complications of IABP. Vascular injury includes loss of peripheral pulse, pain in the leg, neurologic complications, thromboembolism and amputation. The observed frequency was highest in insulin-dependent diabetic and least in nondiabetic

TABLE III Frequency and Severity of Complications in Diabetic and Nondiabetic Patients

	Diabetic Pts			
	Insulin-Dependent (n = 35)	Noninsulin-Dependent (n = 97)	Nondiabetic Pts (n = 601)	
Complications*	No.† (%)	No. (%)	No. (%)	p Value‡
Vascular	12 (34)	17 (18)	82 (14)	0.003
Loss of peripheral pulse	14 (40)	15 (15)	77 (13)	0.0001
Pain in the leg	8 (23)	7 (6)	24 (4)	0.00001
Neurologic complications	5 (13)	2 (2)	16 (3)	0.03
Thrombosis, emboli	11 (31)	11 (11)	57 (9)	0.01
Amputation	1 (3)	0 (0)	3 (0.4)	—
Infectious	13 (37)	21 (22)	148 (25)	0.18
Fever	9 (26)	19 (20)	135 (22)	0.14
Local wound infection	8 (23)	4 (4)	26 (4)	0.00001
Bacteremia	0 (0)	3 (3)	9 (1)	—
Bleeding	5 (14)	17 (18)	83 (14)	0.6
Severity category				
I	6 (15)	20 (18)	93 (13)	
II	18 (45)	31 (27)	178 (25)	
III	4 (10)	2 (2)	22 (3)	
IV	0 (0)	3 (3)	3 (0.5)	

* Some patients had more than 1 complication.
† Number of insertions of balloon pump.
‡ In computing the p value, the frequency of individual complications was weighted by their respective severity (coded by categories I through IV).

TABLE IV Frequency of Vascular Complications in Diabetic and Nondiabetic Patients Stratified by Sex

	Diabetic Pts			
	Insulin-Dependent	Noninsulin-Dependent	Nondiabetic Pts	
Sex	No. (%)	No. (%)	No. (%)	p Value
F	6/18 (33)	9/35 (26)	25/133 (19)	0.3
M	6/17 (35)	8/62 (13)	57/468 (12)	0.02
p value	0.7	0.2	0.03	

TABLE V Hospital Survival in Diabetic and Nondiabetic Patients According to Sex

	Diabetic Pts		
	Insulin-Dependent	Noninsulin-Dependent	Nondiabetic Pts
Sex	Survivors (%)	Survivors (%)	Survivors (%)
M	8/17 (47)	38/62 (61)	286/468 (62)
F	12/18 (67)	17/35 (49)	64/133 (48)
Total	20/35 (57)	55/97 (57)	350/601 (58)

TABLE VI Distribution of Survival in Diabetic and Nondiabetic Patients According to Preexisting Conditions

	Diabetic Pts	Nondiabetic Pts	
Condition	No. (%)	No. (%)	p Value
AMI	33/60 (55)	161/264 (61)	0.3
CAD	54/91 (60)	245/375 (65)	0.2
CHF	17/34 (50)	54/119 (45)	0.6
CVA	4/8 (50)	21/37 (57)	0.7
PVD	3/11 (27)	14/26 (54)	0.1
SH	37/64 (58)	123/192 (64)	0.3
VHD	3/9 (33)	18/46 (39)	0.7

Abbreviations as in Table I.

patients. Vascular complications are more frequent among women than men (19 vs 12%) in the nondiabetic population, but this difference disappeared in the presence of insulin-dependent diabetes (Table IV). However, among all diabetic patients, the complication rate for women is higher than for men (28 vs 18%, difference not significant). The outcome for those patients with vascular complications was generally favorable. Those with less than complete recovery included 3 patients with pain in the leg who subsequently had femoral angioplasty, 1 patient with neurologic damage who had residual footdrop, 1 patient with thrombosis or emboli who died during femoral embolectomy and 1 patient who required above-the-knee amputation.

The second most frequent type of complication was infectious, which includes fever, local infection and bacteremia. The higher rate of infectious complications in insulin-dependent diabetic patients (37%) was largely due to the relatively high rate of local infections in this group. Bacteremia among diabetic patients was associated with the worst outcome, and 2 of 3 died.

The rate of infectious complications among all patients varied according to where circulatory assistance was initiated: 12% for those patients in whom IABP was initiated in the operating room; 17% in the catheterization laboratory; and 25% in the cardiac or surgical intensive care unit.

Seventy-five diabetic patients (57%) were discharged alive from the hospital after IABP, which was essentially the same proportion as among nondiabetic patients (Table V and VI). Although survival varied according to sex and type of diabetes (Table VI), none of the differences reached statistical significance.

The influence of prior medical history on survival of diabetic and nondiabetic patients is listed in Table VI. The survival of patients in both groups was nearly the same for all antecedent conditions except peripheral vascular disease. Table VII shows survival according to the indication for assisted circulation. Again, diabetic patients fared essentially as well as nondiabetics, except for those with unstable angina. Only 72% of the diabetic patients in the latter group were alive at hospital discharge compared with 88% of the nondiabetic patients.

Definition of patient subset by logistic regression analysis: Logistic regression models that attempted to find combinations of predictor variables (demographics, preexisting condition, indication and duration of

IABP support) to explain complications (categorized into severity of symptom subgroups) were of limited value. When a second or third predictor was entered into a model, only a very minor additional variation in the complication was accounted for in comparison with the amount of variation accounted for by a single predictor variable. Further, when combinations of symptoms (for a given complication) and predictor variables were considered, the sample sizes were usually too small to make the logistic model stable.

Discussion

The frequency of overt DM in the U.S. is about 3 to 4%.[12] Among our group of IABP patients the frequency was 18% (Table VIII), which is consistent with the high frequency of coronary artery disease[13] and myocardial infarction in diabetics.[5] In those with severe diabetes, the incidence of cardiac disorders may be 2 or 3 times that of the general population. Women with diabetes are said to be at especially high risk.[2,14] This is consistent with our findings: 40% of diabetic patients requiring balloon pumping were women, whereas among nondiabetics only 23% were women.

As in other series,[15,16] vascular injuries were common complications of IABP. We found their frequency to be considerably higher among diabetic (22%) than among nondiabetic patients (14%). Insulin-dependent patients accounted for most of this increase; the frequency of vascular damage was 34% in this group. Although there was a significant difference in the incidence of vascular complications between male and female patients among the nondiabetics, an observation related to the size of the femoral artery in the female,[17] it did not reach statistical significance in the diabetic patients. On the other hand, male diabetic patients showed significant changes in the rate of vascular complications compared with nondiabetic men; these changes were not achieved in the female population. This finding may be related to the degree of peripheral vascular disease in diabetic men.[18] Most patients with vascular complications eventually recovered completely. As in other series,[19,20] the amputation rate was <1%.

The rate of local wound infection was also significantly higher in diabetic (9%) compared with nondiabetic patients (4%). Various investigators have demonstrated defective function of polymorphonuclear leukocytes in both adult and juvenile diabetics,[21–23] a finding that may account for the predisposition of such patients to infection.

The question of whether the use of a percutaneous balloon would alter any of these findings is timely. In this retrospective study it was not possible to determine this because the selection of the type of balloon used was based in part on the condition of the patients. To eliminate this bias, a separate prospective randomized study was carried out[24]; this study concluded that although "percutaneous technique for IABP insertion is faster than the surgical technique, and technically easy, it is associated with a higher incidence of vascular complications."

TABLE VII Survival in Diabetic and Nondiabetic Patients According to Indication for Balloon Pumping

	Diabetic Pts		Nondiabetic Pts		
Indication	Survivors/ Affected	(%)	Survivors/ Affected	(%)	p Value
AMI	6/16	(38)	50/89	(56)	0.1
Arrhythmia	1/2	(50)	7/19	(33)	—
Catheterization support	1/2	(50)	6/7	(86)	—
CHF	9/19	(47)	25/53	(47)	0.9
Low CO	4/5	(80)	17/28	(61)	—
MR	0/2	(0)	10/22	(46)	—
PO pump failure	1/6	(17)	15/33	(46)	—
Preoperative support	24/29	(83)	102/124	(82)	0.9
Shock	12/35	(34)	50/163	(31)	0.6
Unstable angina	26/36	(72)	117/133	(88)	0.02
VSD	0/2	(0)	5/18	(28)	—
Weaning from oxygenator	4/9	(44)	22/58	(38)	0.7

Abbrevations as in Tables I and II.

TABLE VIII Prevalence of Diabetes Mellitus

	In Balloon Pump Series		In General Population*
	No.	(%)	(%)
Insulin-dependent	35	(4.8)	(0.6–1.3)
Noninsulin-dependent	97	(13.2)	(2.7)
Total	132	(18.0)	(3.3–4.0)

* From reference 12.

Heart disease is the most frequent cause of death among diabetic subjects.[25] The mortality rate of diabetic subjects is almost 3 times that of the general population, and for each specified cardiovascular cause, mortality is distinctly higher among diabetics.[18] In our diabetic patients, the 57% overall survival rate did not differ from that of nondiabetics (58%, $p = 0.6$). As in the nondiabetic, the diabetic woman had a lower survival rate (55%) than the diabetic man (58%), although the difference was not significant. Insulin dependence does not appear to influence the probability of survival. The fact that most diabetic patients in this series were in adequate control of their condition may account for this finding.[14]

These data support the conclusion that DM increases the risk of minor vascular and infectious complications associated with IABP, especially for insulin-dependent patients. This agrees with the expectation that diabetes is an important complicating factor. However, since we did not obtain evidence that the risk of permanent sequelae is significantly higher among diabetic patients, and survival for diabetic and nondiabetic patients is the same, the implication is that IABP is not contraindicated in diabetic subjects. In addition, the higher incidence of infectious complications suggests that operating room standards for sterility be used whenever balloon pump insertion is attempted in diabetic patients.

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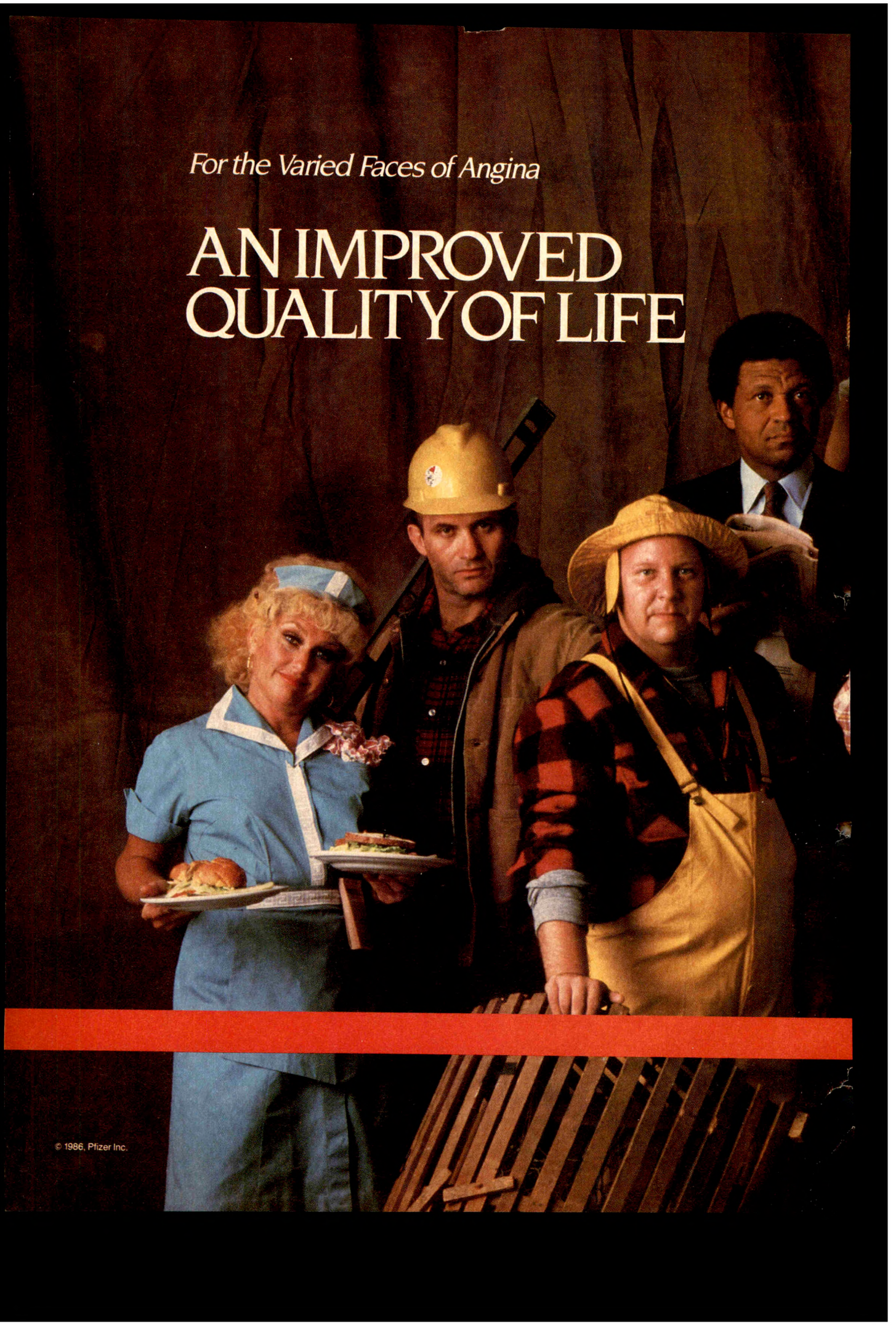
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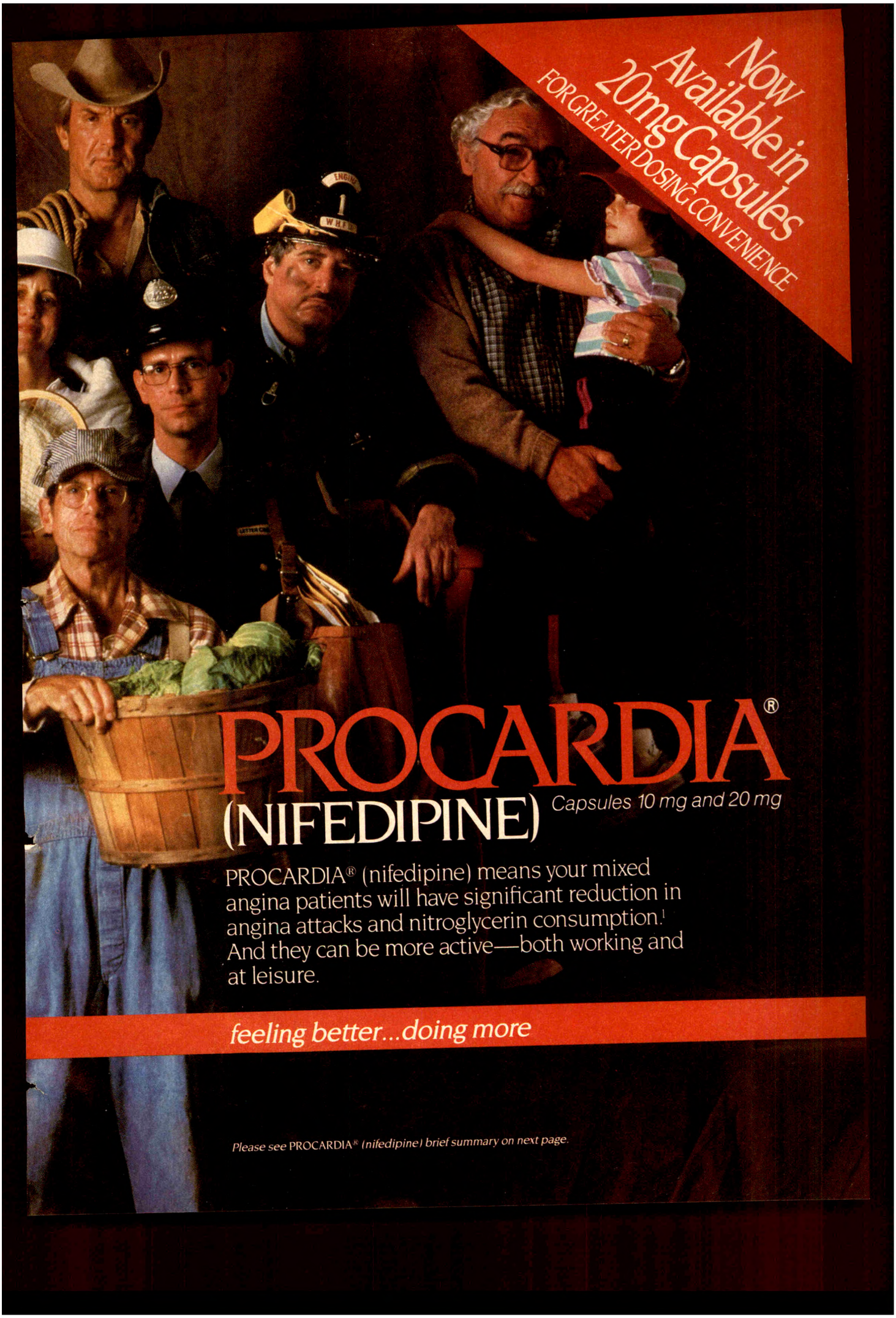
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Because PROCARDIA decreases peripheral vascular resistance (occasional patients have had excessive hypotension), careful monitoring of blood pressure during initial administration and upward dosage titration is suggested, especially for patients taking other drugs known to lower blood pressure. Occasional patients have developed increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases.

–Offers a favorable safety profile

Most frequently reported side effects associated with PROCARDIA therapy, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients; transient hypotension in about 5%; palpitation in about 2%; syncope in about 0.5%.

Reference:
1. Stone PH, Muller JE, Turi ZG, et al: Efficacy of nifedipine therapy in patients with refractory angina pectoris: Significance of the presence of coronary vasospasm. *Am Heart J* 1983; 106:644-652.

Brief Summary
PROCARDIA® (nifedipine) Capsules For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting PROCARDIA or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Laboratory tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to PROCARDIA therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have been reported.

Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some PROCARDIA (nifedipine) patients. No clinical significance for these findings has been demonstrated. Positive direct Coombs test with/without hemolytic anemia has been reported.

Although PROCARDIA has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare, reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to PROCARDIA therapy is uncertain in most cases but probable in some.

Drug interactions: Beta-adrenergic blocking agents: (See INDICATIONS AND WARNINGS.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Coumarin anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom PROCARDIA was administered.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%) after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats and embryotoxic in rats, mice and rabbits. There are no adequate and well controlled studies in pregnant women. PROCARDIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: The most common adverse events include dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, shortness of breath, diarrhea, constipation, gastrointestinal cramps, flatulence, inflammation, joint stiffness, shakiness, jitteriness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties, thrombocytopenia, anemia, leukopenia, purpura, allergic hepatitis, gingival hyperplasia, depression, paranoid syndrome, transient blindness at the peak of plasma level, erythromelalgia, and arthritis with ANA (+). Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

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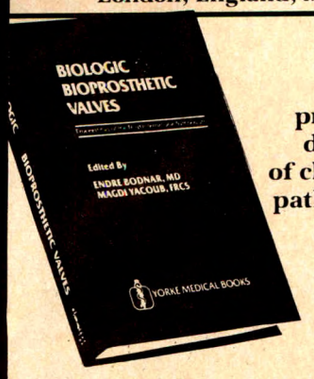

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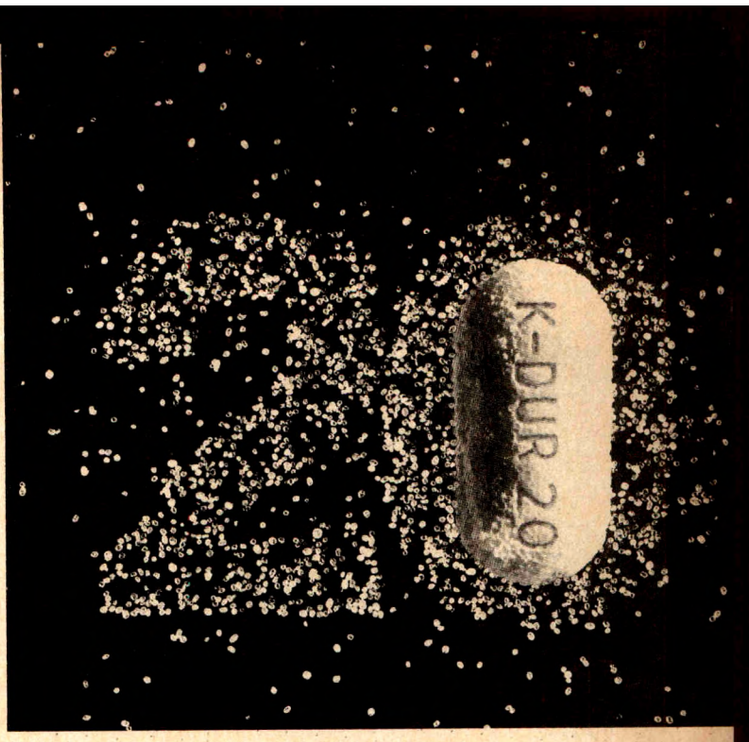

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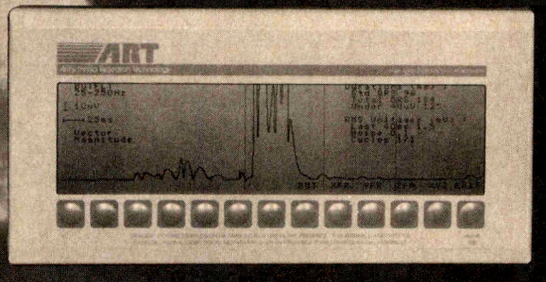

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[1]Gomes, A.J., et al. A New Noninvasive Index to Predict Sustained Ventricular Tachycardia and Sudden Death in the First Year After Myocardial Infarction: Based on Signal-Averaged Electrocardiogram, Radionuclide Ejection Fraction and Holter Monitoring. Journal of the American College of Cardiology 10 (2) 349-57. August 1987. Additional references available.

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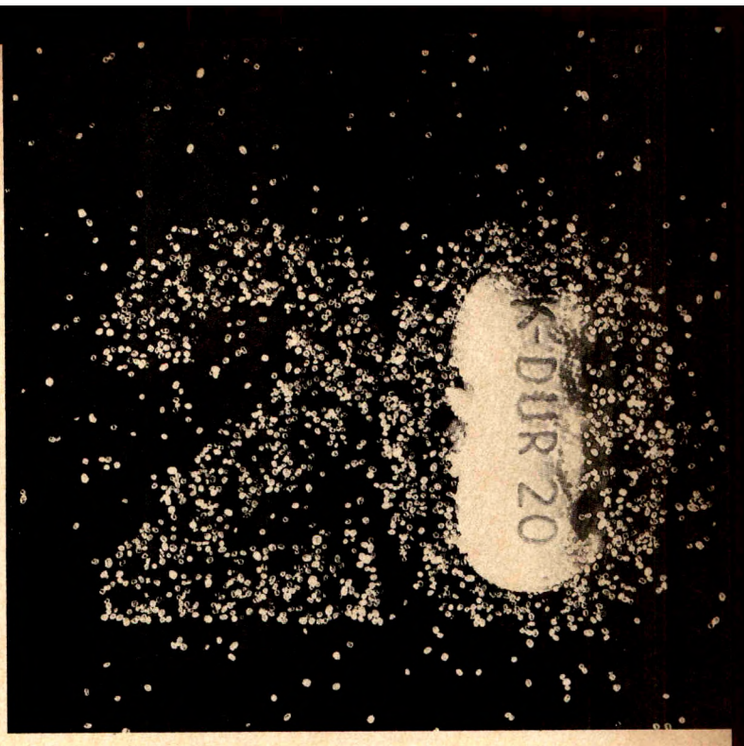

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K-DUR™ Microburst Release System™
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INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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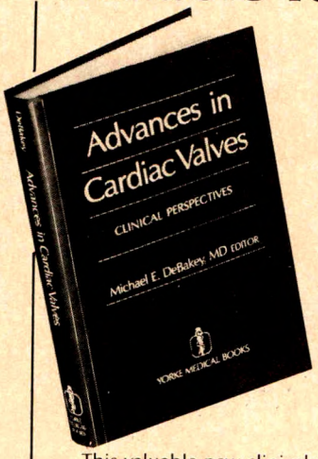

Advances in Cardiac Valves
Clinical Perspectives

edited by
Michael E. DeBakey, MD

0-914316-40-0, November 1983, 274pp., $35.00

This valuable new clinical reference provides a detailed update on many aspects of mechanical heart valve prostheses, including hemodynamics, clinical results, results in children, non-invasive assessments, special indications, and implant techniques. Each topic is presented in an easily understood style and format which facilitate the comprehension of recent developments in heart valve replacement for the busy clinician.

Each chapter is written by internationally respected physicians and medical scientists each of whom is pre-eminent in his field. All of this information has been co-ordinated by Dr. DeBakey to produce a very readable and informative volume on the state-of-the-art of heart valve replacement with mechanical prostheses. No cardiologist, cardiovascular surgeon, internist, or bioengineer can afford *not* to be knowledgeable about the information in this book.

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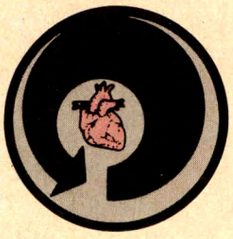

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6:30 pm-10:00 pm Symposium (Marquis Ballroom I & II)
10:00 pm-11:00 pm Reception With Faculty

Chairman: Eugene Braunwald, MD

Renin-Angiotensin System and the Heart — *Victor J. Dzau, MD, FACC*

The Status of Neurohormonal Research in Heart Failure and Myocardial Ischemia — *Robert J. Cody, MD*

Free Radicals and Reperfusion-Induced Myocardial Injury — *Robert Kloner, MD, PhD*

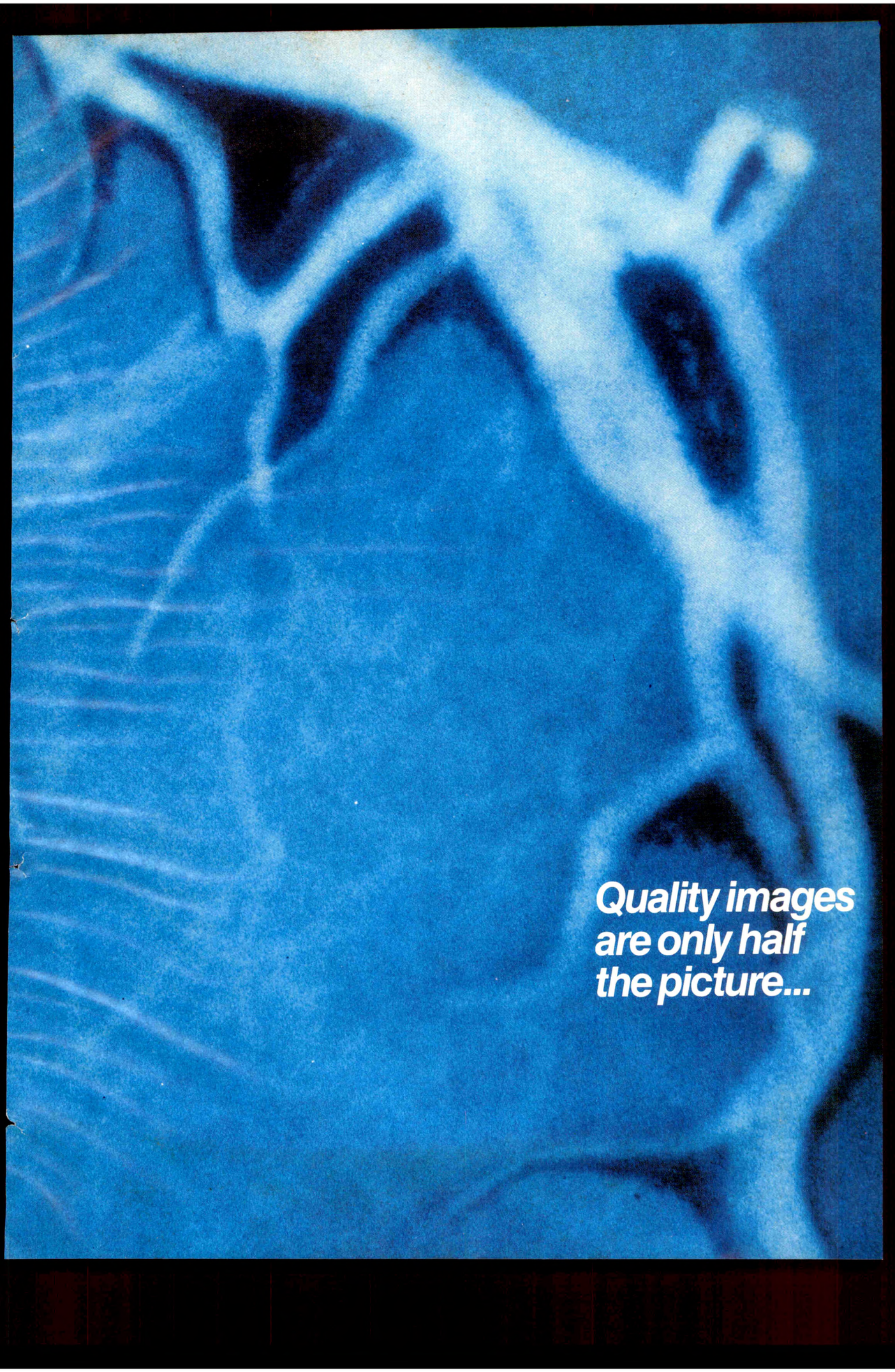
Remodeling of the Ventricle Following Myocardial Infarction — *Cees Visser, MD*

Prognostic Significance of Ventricular Enlargement — *Harvey D. White, MB ChB, FRACP*

Attenuation of Ventricular Enlargement Following Myocardial Infarction — Effect of Captopril — *Gervasio Anthony Lamas, MD*

Survival and Ventricular Enlargement Following Acute Myocardial Infarction — *Marc A. Pfeffer, MD, PhD*

On-site registration will be held outside the Marquis Ballroom.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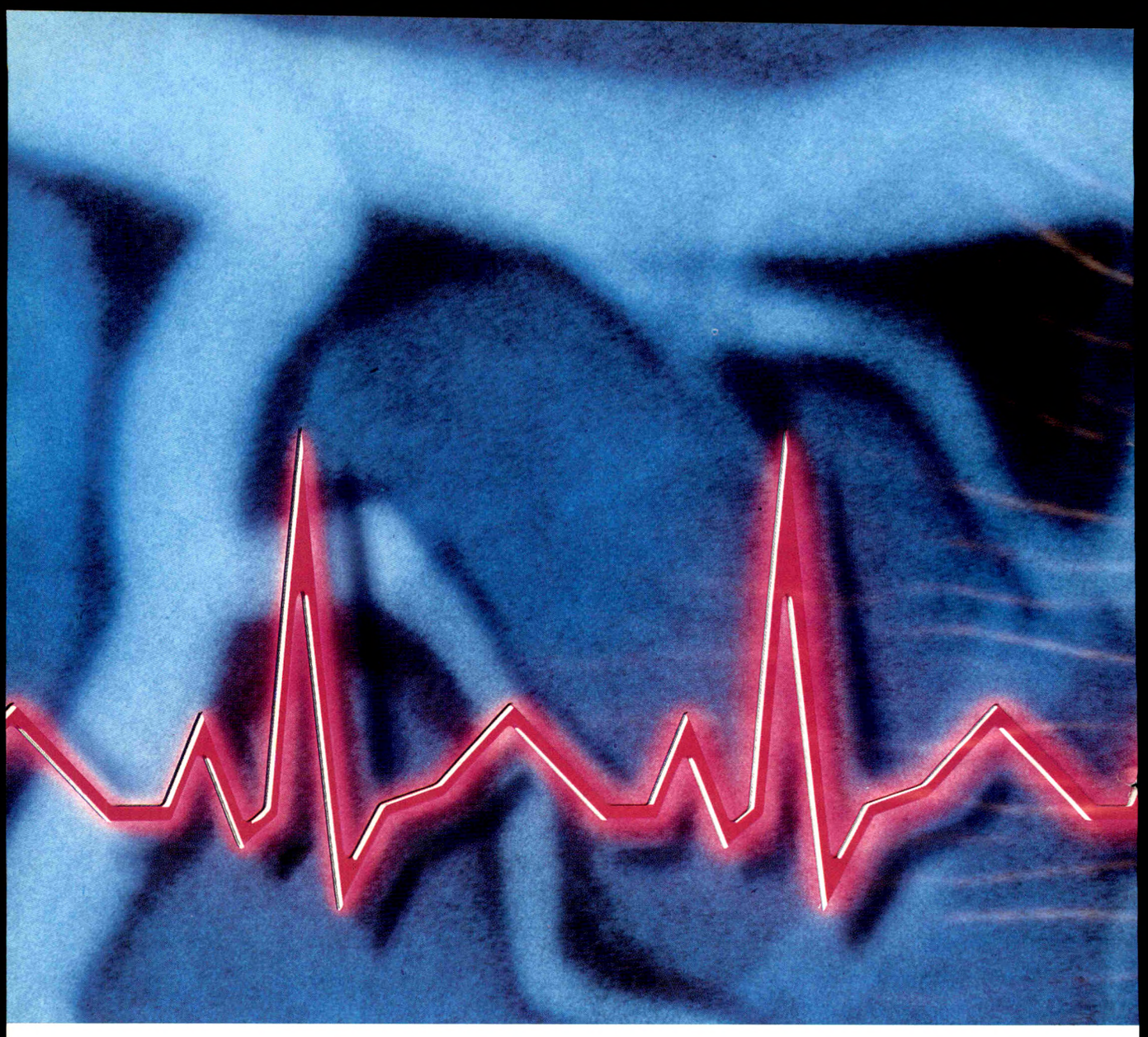

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Hexabrix offers less interference with cardiac function and less risk of nephrotoxicity when compared with conventional contrast media.[1-4] This is particularly important for procedures such as PTCA, where larger volumes of contrast media are necessary.

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Of the three newer contrast agents, Hexabrix offers the lowest osmolality per milligram of iodine (600 mOsm/kg H_2O, versus 796 mOsm for iopamidol-370 and 844 mOsm for iohexol-350). The lower osmolality of Hexabrix reduces undesirable fluid shifts into the vascular space.

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Studies have demonstrated that Hexabrix has a stronger inhibitory effect on red blood cell clotting *in vitro* than iopamidol or iohexol.[5,6]

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Hexabrix provides a lower viscosity than iohexol-350 or iopamidol-370, for ease of injection, especially in higher-volume procedures.

Please see the following page for references and brief summary of prescribing information.

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CONTRAINDICATIONS

HEXABRIX is contraindicated for use in myelography. Refer to PRECAUTIONS concerning hypersensitivity. Hysterosalpingography should not be performed during the menstrual period; in pregnant patients; in patients with known infection in any portion of the genital tract; or in patients in whom cervical conization or curettage has been performed within 30 days. Arthrography should not be performed if infection is present in or near the joint.

WARNINGS

Serious or fatal reactions have been associated with the administration of iodine containing radiopaque media. It is of utmost importance to be completely prepared to treat any contrast medium reaction.

As with any contrast medium, serious neurologic sequelae, including permanent paralysis, can occur following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord. The injection of a contrast medium should never be made following the administration of vasopressors, since they strongly potentiate neurologic effects.

In patients with subarachnoid hemorrhage, a rare association between contrast administration and clinical deterioration, including convulsions and death, has been reported. Therefore, administration of intravascular iodinated contrast media in these patients should be undertaken with caution.

A definite risk exists in the use of intravascular contrast agents in patients who are known to have multiple myeloma. In such instances anuria has developed, resulting in progressive uremia, renal failure and eventually death. Although neither the contrast agent nor dehydration has separately proved to be the cause of anuria in myeloma, it has been speculated that the combination of both may be a causative factor. The risk in myelomatous patients is not a contraindication to the procedure; however, partial dehydration in the preparation of these patients for the examination is not recommended since this may predispose to precipitation of myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over 40, should be considered before instituting intravascular administration of contrast agents.

Administration of radiopaque materials to patients known or suspected to have pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for treatment of a hypertensive crisis should be available.

Since intravascular administration of contrast media may promote sickling in individuals who are homozygous for sickle cell disease, fluid restriction is not advised.

In patients with advanced renal disease, iodinated contrast media should be used with caution and only when the need for the examination dictates, since excretion of the medium may be impaired. Patients with combined renal and hepatic disease, those with severe hypertension or congestive heart failure and recent renal transplant recipients present an additional risk.

Renal failure has been reported in patients with liver dysfunction who were given an oral cholecystographic agent followed by an intravascular iodinated radiopaque agent and also in patients with occult renal disease, notably diabetics and hypertensives. In these classes of patients there should be no fluid restriction and every attempt made to maintain normal hydration prior to contrast medium injection, since dehydration is the single most important factor influencing further renal impairment.

Caution should be exercised in performing contrast medium studies in patients with endotoxemia and/or those with elevated body temperatures.

Reports of thyroid storm occurring following the intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, suggest that this additional risk be evaluated before use of this drug. Iodine-containing contrast agents may alter the results of thyroid function tests which depend on iodine estimation, e.g., PBI, and may also affect results of radioactive iodine uptake studies. Such tests, if indicated, should be performed prior to the administration of this preparation.

PRECAUTIONS

Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. All procedures utilizing contrast media carry a definite risk of producing adverse reactions. While most reactions are minor, life-threatening and fatal reactions may occur without warning, and this risk must be weighed against the benefit of the procedure. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. If a serious reaction should occur, immediately discontinue administration. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration. (See ADVERSE REACTIONS.)

Preparatory dehydration is dangerous and may contribute to acute renal failure in infants, young children, the elderly, patients with pre-existing renal insufficiency, patients with multiple myeloma, patients with advanced vascular disease and diabetic patients.

Acute renal failure has been reported in diabetic patients with diabetic nephropathy and in susceptible non-diabetic patients (often elderly with pre-existing renal disease) following the administration of iodinated contrast agents. Therefore, careful consideration of the potential risks should be given before performing this radiographic procedure in these patients.

Severe reactions to contrast media often resemble allergic responses. This has prompted the use of several provocative pretesting methods, none of which can be relied on to predict severe reactions. No conclusive relationship between severe reactions and antigen-antibody reactions or other manifestations of allergy has been established. The possibility of an idiosyncratic reaction in patients who have previously received a contrast medium without ill effect should always be considered. Prior to the injection of any contrast medium, the patient should be questioned to obtain a medical history with emphasis on allergy and hypersensitivity. A positive history of bronchial asthma or allergy (including food), a family history of allergy, or a previous reaction or hypersensitivity to a contrast agent may imply a greater than usual risk. Such a history may be more accurate than pre-testing in predicting the potential for reaction, although not necessarily the severity or type of reaction in the individual case. A positive history of this type does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but does call for caution. (See ADVERSE REACTIONS.)

Prophylactic therapy including corticosteroids and antihistamines should be considered for patients who present with a strong allergic history, a previous reaction to a contrast medium, or a positive pre-test since in these patients the incidence of reaction is two to three times that of the general population. Adequate doses of corticosteroids should be started early enough prior to contrast medium injection to be effective and should continue through the time of injection and for 24 hours after injection. Antihistamines should be administered within 30 minutes of the contrast medium injection. Recent reports indicate that such pre-treatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity. A separate syringe should be used for these injections.

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia which can prolong the circulation time and increase the duration of contact of the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

PRECAUTIONS FOR SPECIFIC PROCEDURES

Pediatric Angiocardiography: It is advisable to monitor for ECG and vital signs changes throughout the procedure.

When large individual doses are administered, sufficient time should be allowed for any observed changes to return to or near baseline prior to making the next injection.

Caution should be used when making right heart injections in patients with pulmonary hypertension or incipient heart failure, since this may lead to increased right side pressures with subsequent bradycardia and systemic hypotension. Patients with pulmonary disease present additional risks.

Caution is advised in cyanotic infants since apnea, bradycardia, other arrhythmias and a tendency to acidosis are more likely to occur.

Since infants are more likely to respond with convulsions than are adults, the amount of total dosage is of particular importance. Repeated injections are hazardous in infants weighing less than 7 kg, particularly when these infants have pre-existing compromised right heart function or obliterated pulmonary vascular beds.

Selective Coronary Arteriography with or without left ventriculography: During the administration of large doses of HEXABRIX, continuous monitoring of vital signs is desirable. Caution is advised in the administration of large volumes to patients with incipient heart failure because of the possibility of aggravating the pre-existing condition. Hypotension should be corrected promptly since it may result in serious arrhythmias.

Special care regarding dosage should be observed in patients with right ventricular failure, pulmonary hypertension, or stenotic pulmonary vascular beds because of hemodynamic changes which may occur after injection into the right heart outflow tract.

Peripheral Arteriography: Moderate decreases in blood pressure occur frequently with intra-arterial (brachial) injections. This change is usually transient and requires no treatment; however, the blood pressure should be monitored for approximately ten minutes following injection.

Extreme caution during injection of the contrast agent is necessary to avoid extravasation and fluoroscopy is recommended. This is especially important in patients with severe arterial disease.

Cerebral Angiography: Cerebral angiography should be performed with special caution in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis or embolism, and migraine.

Intra-Arterial Digital Subtraction Angiography: The risks associated with IA-DSA are those usually attendant with catheter procedures. Following the procedure, gentle pressure hemostasis is required, followed by observation and immobilization of the limb for several hours to prevent hemorrhage from the site of arterial puncture.

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

Intravenous Digital Subtraction Angiography: The risks associated with IV-DSA include those usually attendant with catheter procedures and include intramural injections, vessel dissection and tissue extravasation. The potential risk is reduced when small test injections of contrast medium are made under fluoroscopic observation to insure that the catheter tip is properly positioned and, in the case of peripheral placement, that the vein is of adequate size.

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

Peripheral Venography: Special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system.

Extreme caution during injection of contrast media is necessary to avoid extravasation and fluoroscopy is recommended. This is especially important in patients with severe arterial or venous disease.

Excretory Urography: Infants and small children should not have any fluid restrictions prior to excretory urography. (See WARNINGS and PRECAUTIONS concerning preparatory dehydration.)

Contrast Enhancement in Body Computed Tomography: Patient cooperation is essential since patient motion, including respiration, can markedly affect image quality. The use of an intravascular contrast medium can obscure tumors in patients undergoing CT evaluation of the liver, resulting in a false negative diagnosis. Dynamic CT scanning is the procedure of choice for malignant tumor enhancement.

Arthrography: Strict aseptic technique is required to prevent the introduction of infection. Fluoroscopic control should be used to insure proper introduction of the needle into the synovial space and prevent extracapsular injection. Aspiration of excessive synovial fluid will reduce the pain on injection and prevent the dilution of the contrast agent. It is important that undue pressure not be exerted during the injection.

Hysterosalpingography: Caution should be exercised in patients suspected of having cervical or tubal carcinoma to avoid possible spread of the lesion by the procedure. Delayed onset of pain and fever (1-2 days) may be indicative of pelvic infection.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to evaluate carcinogenic potential. However, animal studies suggest that this drug is not mutagenic and does not affect fertility in males or females.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to two times the maximum adult human dose and have revealed no evidence of impaired fertility or harm to the fetus due to HEXABRIX. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Ioxaglate salts are excreted unchanged in human milk. Because of the potential for adverse effects in nursing infants, bottle feedings should be substituted for breast feedings for 24 hours following the administration of this drug.

Pediatric Use: Safety and effectiveness in children has been established in pediatric angiocardiography and intravenous excretory urography. Data have not been submitted to support the safety and effectiveness of HEXABRIX in any other indication. (Precautions for specific procedures receive comment under that procedure.)

ADVERSE REACTIONS

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physiochemical properties of the contrast media, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

NOTE: Not all of the following adverse reactions have been reported with HEXABRIX. Because HEXABRIX is an iodinated intravascular contrast agent, all of the side effects and toxicity associated with agents of this class are theoretically possible, and this should be borne in mind when HEXABRIX is administered.

Severe: life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred following the administration of HEXABRIX as well as other iodine-containing contrast agents. Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature, reported deaths from the administration of conventional iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent).

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, or myocardial ischemia or infarction may occur during coronary arteriography and left ventriculography.

The most frequent adverse reactions are nausea, vomiting, facial flush and a feeling of body warmth. These are usually of brief duration. In double-blind clinical trials, HEXABRIX produced less discomfort upon injection (pain and heat) when compared to various other contrast agents. Other reactions include the following:

Hypersensitivity reactions: Dermal manifestations of urticaria with or without pruritus, erythema and maculopapular rash. Dry mouth. Sweating. Conjunctival symptoms. Facial, peripheral and angioneurotic edema. Symptoms related to the respiratory system include sneezing, nasal stuffiness, coughing, choking, dyspnea, chest tightness and wheezing, which may be initial manifestations of more severe and infrequent reactions including asthmatic attack, laryngospasm and bronchospasm with or without edema, pulmonary edema, apnea and cyanosis. Rarely, these allergic-type reactions can progress into anaphylaxis with loss of consciousness, coma, severe cardiovascular disturbances, and death.

Cardiovascular reactions: Generalized vasodilation, flushing and venospasm. Occasionally thrombosis or, rarely, thrombophlebitis. Extremely rare cases of disseminated intravascular coagulation resulting in death have been reported. Severe cardiovascular responses include rare cases of hypotensive shock, coronary insufficiency, cardiac arrhythmia, fibrillation and arrest. These severe reactions are usually reversible with prompt and appropriate management; however, fatalities have occurred.

Technique reactions: Extravasation with burning pain, hematomas, ecchymosis and tissue necrosis, vascular constriction due to injection rate, thrombosis and thrombophlebitis.

Neurological reactions: Spasm, convulsions, aphasia, syncope, paresis, paralysis resulting from spinal cord injury and pathology associated with the syndrome of transverse myelitis, visual field losses which are usually transient but may be permanent, coma and death.

Other reactions: Headache, trembling, shaking, chills without fever, hyperthermia and lightheadedness. Temporary renal shutdown or other nephropathy.

Pediatric angiocardiography has been complicated by intramural injection with marked adverse effects on cardiac function.

During selective coronary arteriography with or without left ventriculography, patients may have clinically insignificant ECG changes. The following adverse effects have occurred in conjunction with the administration of iodinated intravascular contrast agents for this procedure: hypotension, shock, anginal pain, myocardial infarction, cardiac arrhythmias (bradycardia, ventricular tachycardia, ventricular fibrillation) and cardiac arrest. Fatalities have been reported. Complications to the procedure include dissection of coronary arteries, dislodgement of atheromatous plaques, perforation, hemorrhage and thrombosis.

Following peripheral arteriography, hemorrhage and thrombosis have occurred at the puncture site of the percutaneous injection. Brachial plexus injury has been reported following axillary artery injection.

The major causes of cerebral arteriographic adverse reactions appear to be repeated injections of the contrast material, administration of doses higher than those recommended, the presence of occlusive atherosclerotic vascular disease and the method and technique of injection. Adverse reactions are normally mild and transient. A feeling of warmth in the face and neck is frequently experienced. Infrequently, a more severe burning discomfort is observed. Transient visual hallucinations have been reported. Serious neurological reactions that have been associated with cerebral angiography and not listed under Adverse Reactions include stroke, amnesia and respiratory difficulties. Visual field defects with anopsia and reversible neurological deficit lasting from 24 hours to 48 hours have been reported. Confusion, disorientation with hallucination, and absence of vision sometimes lasting for one week have also been reported. Cardiovascular reactions that may occur with some frequency are bradycardia and either an increase or decrease in systemic blood pressure. The blood pressure change is transient and usually requires no treatment. Arthrography may induce joint pain or discomfort which is usually mild and transient but occasionally may be severe and persist for 24 to 48 hours following the procedure. Effusion requiring aspiration may occur in patients with rheumatoid arthritis. Fever and pain, cramping and tenderness of the abdomen have been reported following hysterosalpingography.

OVERDOSAGE

Overdosages may occur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms may include cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma and cardiac arrest. Treatment of an overdose is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

Ioxaglate salts are dialyzable.

The intravenous LD_{50} values of HEXABRIX (in grams of iodine/kilogram body weight) were 11.2 g/kg in mice, >8 g/kg in rats, >6.4 g/kg in rabbits and >10.2 g/kg in dogs.

DOSAGE AND ADMINISTRATION

Details on dosage are provided in the package insert.
CONSULT FULL PACKAGE INSERT BEFORE USE.
Rev. Jan. 1987

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QRS Morphology-Dependent Pharmacodynamics in Multiform Ventricular Ectopic Activity

KENNETH M. KESSLER, MD, DANEIL McAULIFFE, RN, PATRICIA KOZLOVSKIS, PhD, RICHARD G. TROHMAN, MD, LIAQAT ZAMAN, MD, AGUSTIN CASTELLANOS, MD, RAFAEL SEQUEIRA, MD, and ROBERT J. MYERBURG, MD

The effect of an infusion of intravenous procainamide on the frequency of ventricular premature complexes (VCPs) of differing QRS morphologies was studied in 20 patients with multiform ectopic activity. In 17 of 20 patients, there was differential suppression of single VPCs with different QRS morphologies. VPCs of the most frequent QRS morphology and the second most frequent QRS morphology were compared with respect to the procainamide level at the escape of VPCs from 85% suppression and the duration of suppression measured from the onset of the procainamide infusion. In 8 patients, VPCs of the most frequent QRS morphology remained suppressed at lower procainamide concentrations and for longer times than did VPCs of the second most frequent QRS morphology (escape procainamide concentration = 2.8 ± 1.7 versus 5.4 ± 2.3 μg/ml, p <0.025; time to escape 244 ± 138 versus 98 ± 114 min; p <0.05). In 9 other patients, VPCs of the second most frequent QRS morphology remained suppressed at lower procainamide concentrations and for longer times than did VPCs of the most frequent QRS morphology (escape procainamide concentration 2.9 ± 1.4 versus 8.3 ± 6.3 μg/ml, p <0.025; time to escape 317 ± 114 versus 63 ± 80 min; p <0.001). Thus, in individual patients there are specific patterns of suppression of VPCs of different QRS morphologies which are independent of the frequency of each morphology. There is apparently a differential pharmacologic effect of procainamide on the foci or pathways responsible for the different QRS morphologies of multiform VPCs.

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Both total frequency of ventricular premature complexes (VPCs) and occurrence of specific high-risk forms of ventricular ectopic activity have been used to estimate the risk of potentially lethal ventricular arrhythmias and sudden death.[1-9] Pharmacodynamic studies designed to evaluate the effect of drugs on ventricular ectopic activity and the alteration of risk of potentially lethal arrhythmias are limited. Quantitative suppression of ectopic activity is a goal that may be difficult to achieve,[7,10] and suppression of salvos or nonsustained ventricular tachycardia may be a better therapeutic endpoint in the highest risk groups. The information available on intermediate forms of complex ventricular arrhythmias, such as multiform complexes, is even more limited. It has been suggested that multiform VPCs constitute a risk category intermediate between frequent unifocal VPCs and salvos of 3 or more beats in postmyocardial infarction patients.[11] However, no data are available on the pharmacodynamic responses of multiform VPCs in general or the response of VPCs of different QRS configurations in particular. The present study was designed to evaluate the relation between plasma levels of a model antiarrhythmic agent, procainamide, and the suppression of VPCs of different QRS morphologies in patients experiencing multiform ventricular ectopic activity.

From the Division of Cardiology, Department of Medicine, University of Miami School of Medicine and the Veterans Administration Medical Center, Miami, Florida. This study was supported in part by a grant from the American Heart Association of Greater Miami, Miami, Florida, and by grant HL28130 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Presented in part at the 59th Annual Scientific Sessions of the American Heart Association, Dallas, Texas. Manuscript received August 31, 1987; revised manuscript received October 21, 1987, and accepted October 23.

Address for reprints: Kenneth M. Kessler, MD, Professor of Medicine, Chief, Cardiology Section (111A), VA Medical Center, Medical Service, 1201 N.W. 16th Street, Miami, Florida 33125.

TABLE I Demographic Data

Pt	Diagnosis	Age (yr), Sex	Wt (kg)	CHF	EF (%)	History of VT	Albumin (g%)	Creatinine (mg%)
1	CAD, SH	60, M	96	+	32	0	4.4	1.1
2	DC	74, M	82	+	12	0	3.8	1.4
3	DC	61, M	71	+	20	0	6.0	1.5
4	AMI	64, M	70	0	40	0	4.9	1.5
5	CAD, SH	42, M	72	+	35	+	4.0	0.9
6	CAD	53, M	71	0	15	+	4.5	1.5
7	CAD, MVP, SH	57, M	81	+	80	+	5.2	1.4
8	DC	76, M	76	0	20	0	3.4	2.8
9	AMI	64, M	85	+	35	0	4.5	1.2
10	CAD	65, M	80	0	28	0	4.4	1.2
11	CAD, MVP, SH	29, M	115	0	44	0	3.8	1.2
12	CAD	56, M	82	+	55	0	5.0	1.2
13	COPD	60, M	74	0	35	0	3.1	0.6
14	DC, MVP	79, M	67	+	35	+	3.8	0.8
15	Cholecystitis	63, F	77	0	NA	0	3.9	0.5
16	AMI	74, F	59	+	30	0	4.3	1.0
17	CAD	69, M	62	+	22	+	3.0	1.0
18	AMI	74, F	60	0	32	0	4.2	1.0
19	CAD	69, M	74	+	20	+	3.4	0.9
20		71, M	84	+	16	0	4.3	1.7
	Mean	63	77		32		4.2	1.2
	SD	12	13		16		0.7	0.5

AMI = acute myocardial infarction; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DC = dilated cardiomyopathy; EF = ejection fraction; MVP = mitral valve prolapse; NA = not available; SD = standard deviation; SH = systemic hypertension; VT = ventricular tachycardia.

TABLE II Prospective Evaluation of Spontaneous Percent Decreases of Ventricular Premature Complexes of the Primary (M_1) and Secondary (M_2) Morphologies During the Last 2 Baseline Half-Hour Intervals (3 or 4), Compared to the Mean Total PVC Counts of the First and Second (1 + 2) Half-Hour Intervals

	M_1			M_2		
		Spontaneous Decrease (%)			Spontaneous Decrease (%)	
Pt	Mean (1+2)	(3)	(4)	Mean (1+2)	(3)	(4)
1	295	12	26	10	0	0
2	85	66	91*	12	25	42
3	88	59	85*	4	0	0
4	19	11	0	7	0	8
5	2	0	0	89	38	94*
6	47	28	0	29	0	30
7	48	0	0	25	0	0
8	296	0	0	181	2	0
9	27	0	0	5	0	0
10	84	0	0	12	0	0
11	41	16	36	18	72	56
12	138	0	0	256	66	100*
13	127	0	0	8	0	0
14	393	4	9	43	25	72
15	402	0	0	14	79	93*
16	59	30	42	30	3	10
17	21	0	0	6	0	0
18	196	0	16	12	17	42
19	272	0	0	67	14	11
20	52	0	0	59	59	51

≥85% suppression for 30 minutes in 5 of 80 = 6.25%; ≥95% suppression for 30 minutes in 1 of 80 = 1.25%; ≥ 85% suppression for 60 minutes in 0 of 80 = 0.00%. Criteria for escape of PVCs: Return of >5% or >15% of PVCs for 1 or 2 half-hour intervals, respectively.

0 = either no decrease or an increase in PVCs.

* ≥85% suppression.

Methods

Patient selection: Twenty patients admitted to the coronary care or telemetry units were studied. Entry criteria included: (1) multiform VPCs (see definition later); (2) no contraindication to therapy with a class I antiarrhythmic agent; and (3) no antiarrhythmic agent administered for the preceding 48 hours (or >5 drug half-lives). The history and physical examination were reviewed in detail with specific reference to the cardiovascular diagnosis and presence of transient arrhythmogenic factors (e.g., acute ischemia, hypoxia, hypokalemia, aminophylline use). Patients had a clinical indication for antiarrhythmic therapy and informed consents were obtained from each. All were at steady state and no changes in therapy were instituted during the study protocol.

Treatment protocol: A 2-channel ambulatory monitor was used to record continuous rhythm data before, during and after antiarrhythmic intervention. After a 2-hour baseline recording, procainamide hydrochloride was infused intravenously (25 mg/min) to 1 of the following endpoints: (1) 100 mg more than the dose required for 100% VPC suppression or (2) 1,000 mg total dose. In no case was dosing limited due to toxicity (e.g., hypotension, QRS prolongation or proarrhythmic effect). Blood samples were obtained for procainamide and N-acetyl procainamide concentrations at baseline and hourly after the onset of drug administration for 6 to 8 hours. Longer baseline observations, although preferable, were deemed clinically inappropriate because a need to treat had been determined.

Analysis of arrhythmia recordings: Ambulatory recordings were made on a 2-channel recorder and

transcribed using a computerized system (Del-Mar Avionic Heart Screen II). The initial analysis was semiautomated, with preselection of counting criteria done by 1 or more of the authors experienced in arrhythmia interpretation and monitoring techniques; extensive real-time counting was necessary. The frequency of VPCs of each QRS morphology subset was counted and logged by half-hour intervals. The characterization of VPC-QRS morphologies required identical QRS configuration in both monitor leads as determined by the Del-Mar algorithm and confirmed by visual inspection. Pharmacodynamic data were analyzed for VPCs of the most frequent and second most frequent QRS morphologies.

Antiarrhythmic drug analysis: All blood samples were transferred promptly to our research laboratory and centrifuged. Albumin was quantitated by a commercial kit (SIGMA Chemical Co.). Procainamide and N-acetyl procainamide were quantitated by gas-liquid chromatography using a nitrogen-phosphorous selective detector (Hewlett-Packard 5710A).[12] The standard error of the estimate for this technique is <5% of the determined value.

Statistical analysis: Definitions used for the statistical modeling of the pharmacodynamic data included: (1) *baseline frequency*, defined as the average number of VPCs during the 4 half-hour predrug baseline recording intervals; (2) *time to escape*, referred to reemergence of ventricular ectopic activity after suppression by procainamide. It was defined as the time in minutes from the onset of the procainamide infusion until the frequency of suppressed VPCs exceeded 15% of the baseline frequency for 2 consecutive half-hour intervals, i.e., suppression falling below 85% (see validation of suppression criteria in the Results section); (3) *concentration at escape*, defined as the plasma concentration of procainamide at the time to escape, extrapolated from the plasma concentration curve; (4) *differential suppression* (i.e., QRS-morphology dependent pharmacodynamics), when the time to escape of the 2 VPCs having different QRS morphologies varied by at least 2 half-hour intervals. Student *t* tests were used to compare group characteristics. Statistical significance was assigned to the $p < 0.05$ level.

Results

Demographic data: There were 17 men and 3 women, mean age 63 ± 12 years. Primary diagnoses included chronic coronary artery disease in 9 patients, idiopathic dilated cardiomyopathy in 5 and acute myocardial infarction in 4. Acute or chronic congestive heart failure complicated the course in 12 of 20 patients. Six had had symptomatic ventricular tachycardia by history. Mean ejection fraction was 32 ± 16%, mean weight 77 ± 13 kg, mean albumin 4.2 ± 0.7 g%, and mean creatinine 1.2 ± 0.5 mg% (Table I).

Validation of suppression criteria: Suppression criteria were derived from prospective analysis of the trends in spontaneous variability of VPCs of the most frequent and second most frequent QRS morphologies during the 2-hour predrug, baseline phase. The predrug period was divided into 4 half-hour intervals and the frequency of VPCs of the most frequent and second most frequent QRS morphology in the third and fourth intervals was compared to the average of the first and second half-hour intervals. A spontaneous decrease of VPC frequency of >85% was observed in only 5 (6.25%) of 80 comparisons (Table II), and the incidence of spontaneous decrease of >95% was only 1.25%. A >85% reduction for both 30-minute intervals was never recorded. Thus, although spontaneous variability was evident, the probability of observing a false positive decrease of VPCs in any 1 half-hour interval was low (and inconsequential when either >85% suppression for 2 continuous half-hour intervals or >95% suppression was considered). On the basis of this observation, the criteria for significant VPC suppression in our patient group was defined as a >85% decrease in VPCs for 2 or more half-hour intervals, or >95% decrease in VPCs for 1 half-hour interval. Conversely, escape of ectopic activity following procainamide suppression study was defined as a return of ectopy to >15% of baseline VPC frequency for 2 half-hour intervals.

Baseline arrhythmia characteristics: Entry criteria required each patient to have 2 or more VPC-QRS morphologies identified on 2-channel full-disclosure ambulatory monitor recordings. There were 2 morphologies in 11 patients, 3 morphologies in 3, 4 morphologies in 3 and 5 or more morphologies in 3 (Table III). However, the 2 most frequent QRS morphologies accounted for >90% of all VPCs in 18 of 20 patients; therefore, only VPCs of the first and second most frequent QRS morphologies were analyzed. The baseline frequency of VPCs of the most frequent QRS morphology averaged 154 ± 148 per hour and of the second most frequent QRS morphology 38 ± 49 per hour. Repetitive forms of >2 VPCs were present in 19 of 20 patients and most frequently were of mixed QRS configurations (Table III).

Pharmacokinetic data: The mean procainamide loading dose was 943 ± 109 mg, with 15 of 20 patients receiving 1,000 mg (Table IV). Peak procainamide concentrations were highly variable, ranging from 5.5 to 24.4 μg/ml. The calculated mean plasma half-life (2.9 ± 0.8 hours), total body clearance (7.3 ± 2.3 ml/min/kg), and apparent steady state volume of distribution (1.8 ± 0.4 liter/kg) were normal. Variations in volume of distribution accounted for only 43% ($r = 0.66$) of the variability in peak levels. Procainamide binding was normal in each patient (60 to 70% unbound fraction). N-acetyl procainamide values were all well below the "therapeutic" range and were not considered in data management (Table IV). The difference in the time to escape of VPCs of the most frequent and second most frequent QRS morphologies was in part related to procainamide half-life ($r = 0.46$, $p < 0.05$).

Pharmacodynamic data of single ventricular premature complexes: Differential suppression of VPCs of the most frequent and second most frequent QRS morphologies was observed in 17 of 20 (85%) patients (Table III). In 8 patients, VPCs of the most frequent QRS morphology (baseline frequency 278 ± 218/hour) were suppressed at a lower procainamide concentration (mean escape concentration 2.8 ± 1.7 μg/ml) and for a longer period of time (mean time to escape 244 ±

TABLE III Pharmacodynamic Data

Pt	No. of QRS Morphologies	PA Concentration at Escape (μg/ml)		Time to Escape (min)		Repetitive Forms	
		M_1	M_2	M_1	M_2	M_1	M_2
1	2	1.8	3.4	210	90	M	M
2	2	0.6	6.0	360	60	M	M
3	2	1.9	2.2	450	360	M	—
5	2	2.7	4.5	150	60	M	M
7	3	4.0	>7.8	180	0	M	M
13	2	4.2	7.1	150	90	M	M
17	2	<1.2	3.4	>390	120	M	M
19	2	5.7	>8.6	60	0	M	M
$M_1>M_2$							
Suppression							
Mean		2.8	5.4*	244	98†		
SD		1.7	2.3	138	114		
4	2	4.7	4.2	180	240	—	—
8	4	>24.4	5.3	0	120	M	M
9	5	>6.9	2.6	0	180	M	—
12	2	6.1	<2.8	90	>390	—	M
14	5	>7.6	<1.5	0	>390	M	M
15	3	>5.7	<1.9	0	>390	U	—
16	4	>10.7	<4.4	0	>390	M	M
18	7	3.4	<1.7	180	>360	M	—
20	4	5.3	<1.9	120	>390	M	M
$M_2>M_1$							
Suppression							
Mean		8.3	2.9*	63	317‡		
SD		6.3	1.4	80	114		
6	3	6.2	6.0	120	150	M	M
10	2	<1.2	<1.2	>390	>390	M	M
11	2	>6.4	>6.4	0	0	M	M
$M_1=M_2$							
Suppression							
Mean		4.6	4.5	170	180		
SD		3.0	2.9	200	197		

* $p < 0.025$; † $p < 0.05$; ‡ $p < 0.001$.

M_1 = VPCs of the most frequent QRS morphology; M_2 = VPCs of the second most frequent QRS morphology; M = repetitive forms of VPCs of mixed (multiform) QRS morphologies; SD = standard deviation; U = repetitive forms of VPCs of uniform QRS morphologies.

138 minutes) than were VPCs of the second most frequent QRS morphology, with baseline frequency 52 ± 50 premature ventricular contractions/hour, mean escape contration of procainamide 5.4 ± 2.3 μg/ml ($p < 0.025$) and mean time to escape 98 ± 114 minutes ($p < 0.05$). Figure 1 shows the percent suppression of VPCs of the most frequent and second most frequent QRS morphologies as a function of procainamide concentrations. In this example, VPCs of the most frequent morphology were more easily and completely suppressed.

In 9 patients, VPCs of the second most frequent QRS morphology (baseline frequency 106 ± 178 VPC/hour) were suppressed at a lower concentration of procainamide (mean escape concentration 2.9 ± 1.4 μg/ml) and for a longer time (mean time to escape 317 ± 114 minutes) than were VPCs of the most frequent QRS morphology, with baseline frequency 400 ± 376 VPC/hour, mean escape concentration of procainamide 8.3 ± 6.3 μg/ml ($p < 0.025$) and mean time to escape 63 ± 80 minutes ($p < 0.001$). Figure 2 shows such a pattern of differential suppression, whereas Figure 3 demonstrates a differential effect without suppression and an apparent increase in the number of VPCs of the most frequent QRS morphology, and at the same time a significant suppression of VPCs of the second most frequent QRS morphology. In 3 patients, there were no differences in the pharmacodynamics of single VPCs of the most frequent and second most frequent QRS morphologies.

Discussion

To study the pharmacodynamics of simple and complex forms of ventricular arrhythmias, both theoretical considerations and empiric observations led us

TABLE IV Pharmacokinetic Data

Pt	Dose (mg)	Procainamide Concentration (μg/ml) Peak (hr)	1	2	3	4	5	6	T½ (hr)	Cl (ml/min/kg)	VD (liter/kg)	NAPA (μg/ml)
1	1,000	5.5	4.3	2.6	2.0	1.6	1.3	1.0	3.0	11.5	3.0	0.3
2	900	11.3	4.0	2.6	2.4	1.9	1.6	1.2	3.2	7.1	2.0	1.5
3	800	10.1	6.1	4.2	3.3	2.6	2.4	2.0	3.3	5.0	1.4	1.7
4	1,000	9.8	6.9	5.7	4.7	4.1	3.1	2.4	3.3	5.8	1.7	1.4
5	1,000	8.6	4.5	2.9	1.7	1.4	1.1	—	2.6	9.9	2.2	1.7
6	1,000	12.6	8.5	6.2	5.7	3.0	3.1	2.6	2.8	5.3	1.3	5.1
7	750	7.8	4.6	3.4	3.2	2.8	2.2	2.0	4.3	4.4	1.6	0.7
8	1,000	24.4	9.9	6.2	5.3	3.9	3.4	2.4	2.7	4.4	1.0	1.7
9	1,000	6.9	4.1	3.4	2.6	1.9	1.2	—	2.3	10.5	2.2	0.6
10	1,000	8.1	6.7	4.6	4.0	2.4	1.5	1.2	1.9	8.4	1.4	1.7
11	1,000	6.4	3.1	2.2	1.5	1.0	0.9	0.8	2.5	9.3	2.0	0.5
12	1,000	9.6	6.1	4.6	3.2	2.8	—	—	2.6	6.8	1.5	0.5
13	1,000	10.7	7.1	4.2	3.9	2.9	2.8	1.3	2.4	6.9	1.4	3.0
14	1,000	7.6	5.2	3.7	2.3	2.0	1.6	1.5	2.8	9.2	2.2	0.8
15	700	5.7	4.4	3.4	2.6	2.0	1.9	—	3.2	6.0	1.7	0.3
16	1,000	10.7	8.2	6.9	6.4	5.3	4.6	4.4	5.3	3.9	1.8	2.4
17	700	14.0	5.5	3.4	2.5	1.8	1.3	1.2	2.4	6.7	1.4	0.6
18	1,000	8.7	6.3	4.9	3.8	2.9	1.8	1.7	2.5	9.5	2.1	1.2
19	1,000	8.6	5.7	3.3	2.4	1.8	1.4	1.0	2.1	9.5	1.7	1.1
20	1,000	14.9	6.8	5.9	4.6	3.3	2.7	1.9	3.0	6.5	1.7	2.3
Mean	943								2.9	7.3	1.8	1.5
SD	109								0.8	2.3	0.4	1.1

Cl = clearance; NAPA = N-acetyl procainamide; SD = standard deviation; T½ = half-life; VD = volume of distribution.

to design this prospective study using multiform ventricular ectopic activity as a model.

Multiform ventricular ectopic activity occupies a central position in the ventricular arrhythmia complexity schema and multiform ectopic activity is frequently associated with repetitive forms.[13–15] However, initiation of the study was hampered by the lack of intrinsic information on the pharmacodynamics of multiform VPCs. Prior studies had grouped multiform VPCs with other complex forms[2–4,8,16,17] and there was a systematic underestimation of multiformity established by reporting only the highest grade of ventricular ectopic activity. Thus, the reported prevalence of multiform VPCs varied from 2%[2] to 92%[16] in high-risk patients. Furthermore, there was disagreement as to the clinical importance of multiformity per se, with some studies supporting multiform VPCs as a risk factor for malignant ventricular arrhythmias or cardiac mortality, or both,[3,5,8,17] while others did not support such a risk.[2] Finally, the mechanism of multiformity also remains undefined. Multiformity may result from either multiple sites of origin (multifocality) or variable exit sites or pathways from the same focus or reentrant circuit. Different sites or different exit pathways may exhibit similar or contrasting responses to pharmacologic intervention. Potentially, clinically important arrhythmias might be suppressed concurrently with suppression of 1 morphology, but not the other(s), and suppression could dissociate from total VPC suppression.

Pharmacodynamic and pharmacokinetic implications: The current study shows that the pharmacodynamic response often differs between the 2 most fre-

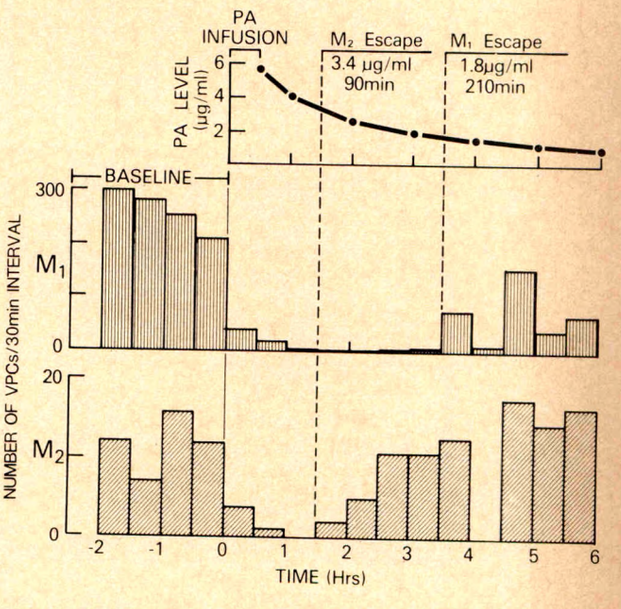

FIGURE 1. Differential suppression of ventricular premature complexes (M1 > M2 sensitivity). The number of ventricular premature complexes (VPCs) of the most frequent (M1) and second most frequent (M2) QRS morphologies is plotted along with simultaneous procainamide (PA) levels for patient 1. VPCs of the most frequent (M1) QRS morphology (mean baseline frequency 534/hour) were suppressed for a longer time (210 minutes) and to a lower procainamide concentration (1.8 μg/ml) than were VPCs of the second most frequent (M2) QRS morphology (mean baseline frequency 24/hour), which suppressed for only 90 minutes and required a procainamide concentration of 3.4 μg/ml for suppression.

quent single VPC-QRS morphologies of multiform pattern. Most of the patients (18 of 20) had organic heart disease, with 6 of 20 previously manifesting life-threatening ventricular arrhythmia. VPCs of >2 QRS morphologies were present in 45% of patients but only 15% of patients had >5 QRS morphologies. The overall VPC frequency was well in excess of the risk threshold of >10/hour suggested for patients with recent myocardial infarction.[18] Morphology-dependent suppression of VPCs was demonstrated in 85% of the patients. Differential suppression favors multiple reentrant circuits or foci rather than variable exits from the same circuit or focus as the mechanism for multiformity in these patients. Suppression of VPCs of the more sensitive QRS morphology occurred at a mean procainamide concentration below the "therapeutic range" (2.9 ± 1.6 μg/ml), whereas the less sensitive form often was not suppressed at procainamide concentrations in the high therapeutic to supra-therapeutic range. The time differential regarding the escape of the 2 morphologies varied from our minimum definition for differential suppression of 60 minutes to greater than 390 minutes and was in part a function of drug half-life. Thus, the occurrence and degree of differential suppression related both to the absolute procainamide concentration achieved and to the rate of decrease during the distribution and elimination phases, implying that the pharmacodynamics of differential suppression might vary as a function of both electropharmacologic and pharmacokinetic parameters in a given individual.

Therapeutic implications: VPCs with varying pharmacodynamic responses to therapy may coexist and there is no therapeutic continuum with respect to ventricular ectopic activity. Such information complements previous data showing differential therapeutic responses of complex and single ectopy as well as differential thresholds for the suppression of VPCs based on clinical setting.[10] The current data suggest that should concordance be established between the suppression of single VPCs and repetitive forms initiated by ventricular complexes of a similar QRS morphology, suppression of specific VPCs may provide individualization of therapy targeted to high-risk tachycardias. When suppression is via VPCs of the less frequent QRS morphology, repetitive form suppression will become independent of statistically significant[19] suppression of total VPCs. Indeed, selective suppression of premature ventricular contraction subsets provides 1 mechanism whereby a high degree of single premature ventricular contraction suppression may not be needed to suppress repetitive forms in selected patients. We conclude that the foci or pathways re-

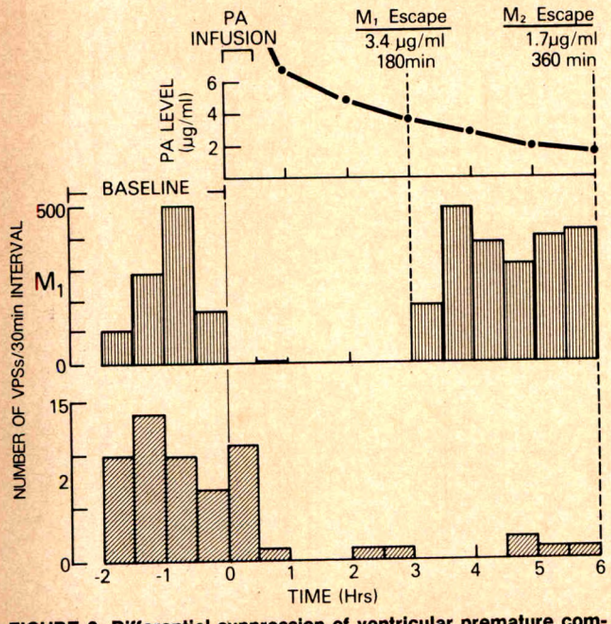

FIGURE 2. Differential suppression of ventricular premature complexes (M2 > M1 sensitivity). The number of ventricular premature complexes (VPC) of the most frequent (M1) and second most frequent (M2) QRS morphologies is plotted along with simultaneous procainamide (PA) levels for patient 18. VPCs of the second most frequent QRS morphology (mean baseline frequency 532/hour) were suppressed for a longer time (>360 minutes) and to a lower procainamide concentration (<1.7 μg/ml) than VPCs of the most frequent (M1) QRS morphology (mean baseline frequency 20/hour), which suppressed for 180 minutes and required a procainamide concentration of 3.4 μg/ml for suppression.

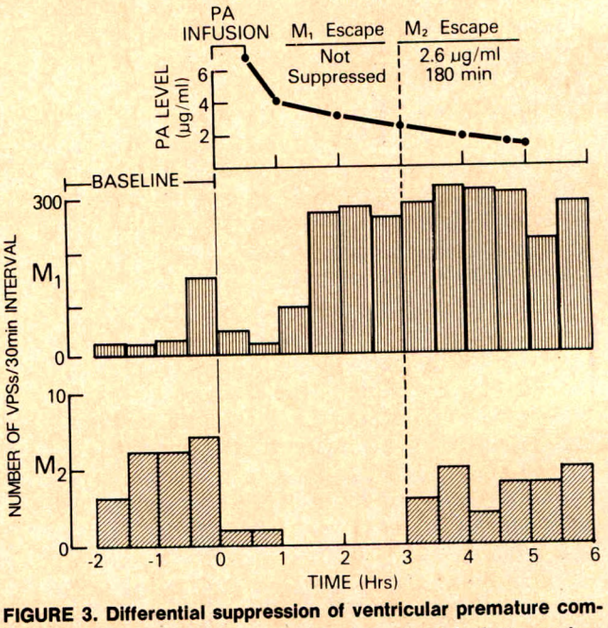

FIGURE 3. Differential suppression of ventricular premature complexes (M2 > M1 sensitivity). The number of ventricular premature complexes (VPC) of the most frequent (M1) and second most frequent (M2) QRS morphologies is plotted along with simultaneous procainamide (PA) levels for patient 9. VPCs of the second most frequent QRS morphology (mean baseline frequency 12/hour) were suppressed for 180 minutes to a procainamide level of 2.6 μg/ml. VPCs of the most frequent QRS morphology (mean baseline frequency 116/hour) showed an increase in frequency after the procainamide infusion (average 526 VPCs/hour from 1 to 6 hours after drug infusion).

sponsible for VPCs of different QRS morphologies appear to have different responses to pharmacologic intervention and that this may relate to endpoints of therapy.

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Tocainide Plus Quinidine for Treatment of Ventricular Arrhythmias

JEAN T. BARBEY, MD, KATHERINE A. THOMPSON, MD, DEBRA S. ECHT, MD, RAYMOND L. WOOSLEY MD, PhD, and DAN M. RODEN, MD

Tocainide and quinidine were administered both as single agents and in combination to 14 patients with chronic ventricular arrhythmias. Therapy with tocainide was limited by the occurrence of dose-related adverse reactions in 8 patients, but could be titrated to a dose that was well-tolerated in 13 of 14 and effective in 2 of 13. The addition of quinidine gluconate to the tolerated dose of tocainide increased the number of patients with arrhythmia suppression from 2 to 6. After tocainide washout, quinidine alone suppressed arrhythmias in only 3 patients. Analysis of electrocardiogram intervals showed that the drugs had additive effects on the coupling interval of the sinus beat to the predominant ectopic beat, but exerted antagonistic effects on the corrected QT interval. These findings suggest that the combination may be clinically useful, exerting pharmacologic effects unlike either agent alone.

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Antiarrhythmic therapy with single agents is frequently only moderately effective and can be limited by the occurrence of adverse effects related to plasma concentrations.[1] Therefore, the strategy of combining drugs to keep doses under those associated with side effects, yet maintain or even increase efficacy, has been advocated. In guinea pig ventricular papillary muscle preparations, Hondeghem and Katzung[2] showed that the combination of lidocaine and quinidine produced supra-additive effects on the $\dot{V}_{max}$ of early extrasystoles but an effect no different from quinidine alone on normal complexes. These data suggested that such combinations might suppress closely coupled abnormal beats while exerting little effect on sodium channels of normal beats. In a group of patients with ventricular arrhythmias, we found that the combination of quinidine and the lidocaine analog mexiletine was more effective and less likely to cause side effects than therapy with either agent alone.[3]

Tocainide, like mexiletine, is a lidocaine analog which can be used orally. In vitro, it blocks the fast inward sodium current and shortens action potential duration.[4] Treatment with tocainide is frequently limited by dose-related neurologic side effects such as tremor or ataxia.[5] Although tocainide and mexiletine produce similar electrophysiologic changes and have comparable side effect profiles, reports from our group and others have suggested that response to 1 lidocaine analog is not predictive of response to the other.[6–8] Tocainide is currently prescribed as a racemic mixture. Of the 2 stereoisomers, the R(−) form is more potent in suppressing arrhythmias in an animal model[9]; however, its plasma concentrations are usually lower than those of the S(+) stereoisomer during tocainide administration in man.[10]

Quinidine also blocks cardiac sodium channels but prolongs the duration of the action potential in most tissues.[11] As with tocainide therapy, side effects during quinidine are frequent and range from diarrhea to arrhythmia aggravation.[12] This study determines if the addition of a low dose of quinidine to tocainide could enhance the efficacy and decrease the toxicity of tocainide given alone and characterizes the antiarrhythmic, pharmacokinetic and electrocardiographic features of this combination.

From the Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee. This study was supported by grants HL36724, GM31304 and RR095 from the United States Public Health Service, Bethesda, Maryland, and from Merck, Sharpe and Dohme, West Point, Pennsylvania. Dr. Barbey was the recipient of a Research Fellowship Award from the American Heart Association (Tennessee Affiliate) during the conduct of this work. Manuscript received September 4, 1987; revised manuscript received and accepted October 27, 1987.

Address for reprints: Dan M. Roden, MD, Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232.

Methods

Adults with >30 ventricular premature complexes (VPCs) per hour over at least 48 hours of ambulatory electrocardiograph recordings were candidates for this trial. Patients with recent myocardial infarction, symptomatic sinus node dysfunction, abnormal conduction or supraventricular arrhythmias were excluded. Tocainide hydrochloride in 400 or 600 mg tablets, quinidine gluconate in 324 mg tablets and identical placebos (all supplied by Merck, Sharp and Dohme) were administered at 8-hour intervals throughout the study.

Study design: Patients were admitted to the Clinical Research Center where, under continuous electrocardiographic monitoring, their antiarrhythmic drug therapies were stopped. After stabilization of arrhythmia frequency with no treatment (and at least 4 elimination half-lives after discontinuation of therapy), placebo administration was begun. Patients whose arrhythmia frequency met entry criteria on placebo continued participating during the rest of the study. There were 4 phases following the placebo run-in, each with a 3-day duration: (1) tocainide 400 mg every 8 hours for each patient; (2) tocainide dose adjustment; (3) treatment with the most effective well-tolerated dosage of tocainide plus 324 mg of quinidine gluconate every 8 hours; and (4) tocainide washout on this dose of quinidine alone.

During the tocainide adjustment phase, the drug was increased to 600 mg every 8 hours if arrhythmias were not suppressed and side effects were absent, or decreased to 200 mg every 8 hours if side effects were present. On the third day of each treatment phase, arrhythmia frequency was quantified by 24-hour ambulatory electrocardiography. The electrocardiogram intervals were measured from a 12-lead recording and trough plasma samples were collected. Quinidine plasma concentrations were determined by reverse-phase high-pressure liquid chromatography. A stereospecific gas chromatographic procedure was used to measure concentrations of the R(−) and S(+) stereoisomers of tocainide.

Data analysis: All data are expressed as mean ± standard deviation. Arrhythmias were considered suppressed if ≥70% of total VPCs and ≥95% of runs (defined as ≥3 consecutive VPCs) were abolished. Student *t* test for paired data or 2-way analysis of variance for multiple observations were used to analyze changes during the course of the study with a p value <0.05 required to reject the null hypothesis of equal means. VPC counts were log-transformed prior to analysis. If significant differences among means were detected by analysis of variance, Duncan's test was used for pairwise comparisons.

Results

Patient characteristics: Eleven of the 14 patients who participated in this study were males. Mean age was 60 ± 9 years and left ventricular ejection fraction 35 ± 13%. Seven patients had coronary artery disease, 6 cardiomyopathy and 1 congenital heart disease. The median number of VEDs/hour was 258 (range 69 to 2,361). Runs were present in 12 patients, but occurred more frequently than 1 per hour in only 3. The average number of previously failed antiarrhythmic trials was 2.5 ± 1 per patient; in all 14 patients, a history was elicited that quinidine and procainamide had been ineffective.

Efficacy: Of the 10 patients who completed all 4 phases of the study as described above, only 2 had arrhythmia suppression after a well-tolerated dose of tocainide alone (1,200 mg/day in 1 case, 1,800 mg/day in the other). Addition of quinidine to this same dose of tocainide also suppressed VPCs in these 2 patients as well as in 4 others. After tocainide washout, 3 patients maintained arrhythmia control on quinidine alone, including the 2 in whom a well-tolerated dose of tocainide alone had been effective previously. Three patients could not complete the study because of intolerable side effects (quinidine-related in 2, tocainide-related in 1). The 14th patient received a lower dose of tocainide during concomitant quinidine therapy than during the titration phase because of neurologic side effects attributed to tocainide. VPC counts were significantly reduced by all 3 drug treatments from baseline ($p < 0.01$, analysis of variance), and counts during tocainide and during tocainide and quinidine were significantly less than during low-dose quinidine.

Adverse reactions: Seven of the 14 patients who received therapy with tocainide alone developed neurologic side effects that resolved with decreased dosage. One patient could not complete the study because of abdominal pain which improved only when tocainide was discontinued entirely. Four patients developed side effects while receiving combination therapy. These adverse effects persisted on quinidine alone after tocainide washout in 3 patients.

Plasma drug concentrations: Plasma concentrations associated with efficacy during therapy with tocainide alone (n = 2) were 5.5 and 8.5 μg/ml for total tocainide, 1.3 and 2.6 μg/ml for R(−) tocainide and 4.3 and 5.9 μg/ml for the S(+) isomer. During combination therapy, effective plasma concentrations (n = 6) ranged from 2.8 to 12.9 for total tocainide, 1.0 to 2.7 μg/ml for R(−) tocainide and 1.8 to 7.1 for the S(+) isomer. Low concentrations of S(+) tocainide were present in the plasma of 8 patients at the end of the tocainide washout period. Mean plasma quinidine concentration (Figure 1) after 3 days of treatment rose from 1.5 ± 0.5 μg/ml to 1.9 ± 0.8 μg/ml ($p < 0.05$), 3 days after tocainide withdrawal. On the other hand, there was no significant effect of quinidine on mean plasma tocainide concentration or on the ratio of S(+) to R(−) isomers, which ranged from 1.4 to 5.6.

Changes in electrocardiographic intervals: Therapy with a well-tolerated dose of tocainide shortened the QTc interval significantly compared to baseline ($p < 0.05$). QTc increase during quinidine alone after tocainide withdrawal was also significant ($p < 0.05$), compared to baseline and tocainide values (Figure 2). QRS was unchanged during the study. In contrast to these findings, the coupling interval of sinus beat to the predominant ectopic beat, a potential index of drug

effect on sodium channels[2,3] which was assessable in 6 patients, was significantly prolonged (compared to baseline) only during combination therapy (Figure 3, $p < 0.01$, analysis of variance). Thus, single-agent treatment shortened (tocainide) or prolonged (quinidine) repolarization, whereas sinus-ectopic coupling tended to increase with all treatments and particularly with the combination.

Discussion

Tocainide alone was effective in only 2 of 14 patients participating in this study, whereas quinidine alone was effective in 3. Addition of low-dose quinidine to a tolerated dose of tocainide suppressed arrhythmias in 6 of 13 patients. Moreover, the margin between tocainide plasma concentrations associated with efficacy and those associated with side effects was increased by the addition of quinidine (Figure 4). In this study, the combination was the only effective treatment arm in 3 of 6 patients. Response to higher doses of quinidine was not evaluated as part of this protocol, but these patients had been referred to our institution because of ventricular arrhythmias resistant to quinidine and procainamide. We conclude that the combination of quinidine and tocainide may, in certain cases, be more efficacious than higher doses of

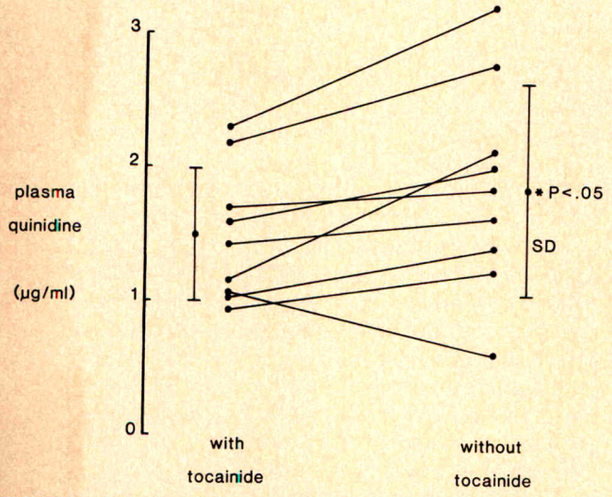

FIGURE 1. Plasma quinidine concentrations during quinidine + tocainide administration (*left*) and following withdrawal of tocainide (*right*).

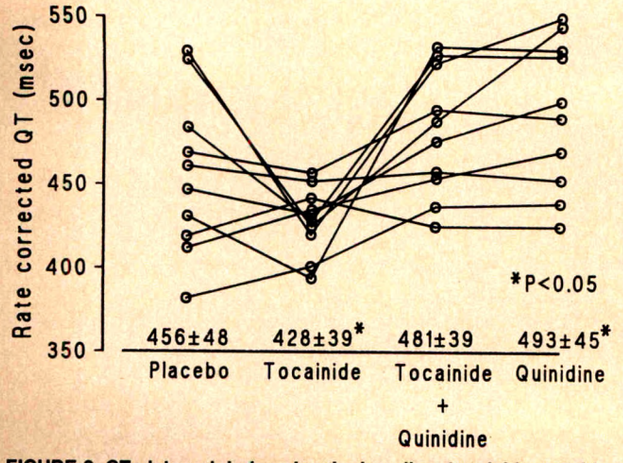

FIGURE 2. QTc interval during placebo baseline, tocainide, combination and quinidine therapy. Mean ± standard deviation for each treatment are shown along with data from each patient. *p <0.05 compared to placebo, analysis of variance.

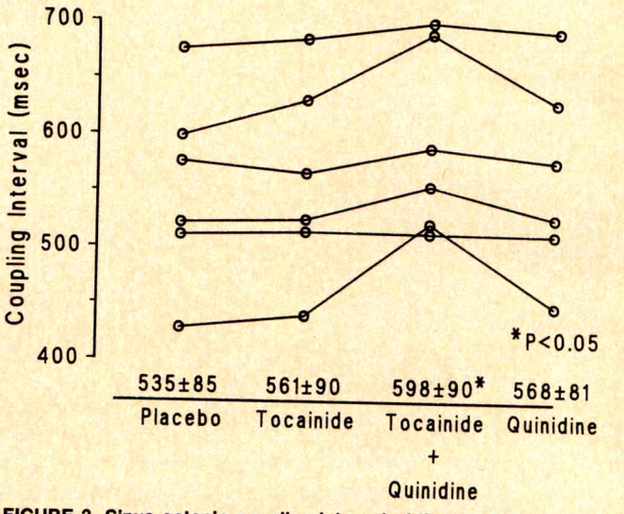

FIGURE 3. Sinus-ectopic coupling interval of the predominant ectopic beat during placebo baseline, tocainide, combination and quinidine therapy. Statistical data as in Figure 2.

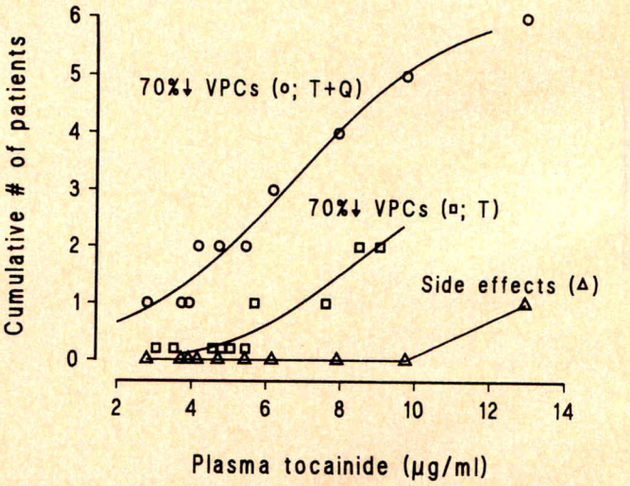

FIGURE 4. Relation between plasma tocainide and cumulative number of patients responding with 70% suppression of ventricular ectopic depolarizations (VPCs) during combined treatment (*open circles*, T + Q) and during tocainide (*squares*, T), as well as those developing side effects during tocainide (*triangles*). Data are shown from the 10 patients completing all 4 treatment arms. The addition of quinidine to tocainide widened the margin between tocainide concentrations associated with efficacy and with toxicity.

either agent alone. Our findings are similar to those reported by Kim et al,[13] who found enhanced efficacy and reduced side effects with the combination in patients with frequent VPCs. In contrast to our study, their design permitted dosage adjustment of either drug at the investigator's discretion at 2-day intervals. They did not report any plasma concentration data and, contrary to our findings discussed later, they detected QRS widening caused by the combination and did not report sinus-ectopic beat coupling interval data.

Plasma quinidine concentrations were slightly higher after tocainide withdrawal than they had been during combination therapy. The explanation for this finding, which requires confirmation, is not known. One possibility is that the rise merely reflected gradual attainment of steady state plasma concentrations between days 3 and 6 of quinidine treatment (although quinidine's elimination half-life of 4 to 16 hours[14] suggests that steady state conditions were indeed present by day 3). The other possibility is that tocainide increased the clearance or the volume of distribution of quinidine by yet unidefined mechanisms. Whatever the interaction mechanism, it did not account for the combination's enhanced efficacy because plasma quinidine concentrations were in fact lower during combination treatment. As previously reported by others,[5] plasma concentration of the S(+) isomer was greater than that of the R(−) isomer in all samples collected. The study design, however, does not allow conclusions to be drawn about the relative contribution of each isomer to the efficacy or the toxicity of tocainide.

Analysis of the electrocardiographic intervals suggests 2 electrophysiologic effects accompanying the increased antiarrhythmic activity noted during combination therapy. At baseline, single morphology VPCs with fixed coupling were present in 6 patients. The combination therapy prolonged this coupling interval to a greater extent than did either agent alone, presumably reflecting an additive effect of the drugs' sodium channel blocking properties. As pointed out by others,[2] the combination of quinidine and lidocaine is particularly attractive because of its potential for greater antiarrhythmic effects at short coupling intervals (or rapid rates) and minimal effect on baseline electrophysiology. Moreover, quinidine's prolonging effect on action potential increases the time sodium channels spend in the inactivated state, thereby theoretically enhancing sodium current depression by drugs which block inactivated channels (such as lidocaine).[15]

In contrast to this additive action on sinus-ectopic coupling, QTc duration measured during combination therapy was found to be intermediate between those observed during treatment with either agent alone. Kim et al[13] also found additive sodium channel effects (QRS widening) and antagonistic QTc effects. Tocainide, by limiting the quinidine-induced prolongation of repolarization, may increase the ratio of the ventricular effective refractory period to the duration of action potential, an effect thought to correlate with antiarrhythmic activity.[16] Thus, electrocardiographic indexes suggest that the favorable interaction noted between quinidine and tocainide has an underlying electrophysiologic basis similar to the previously described quinidine-mexiletine association.[2,3] These effects may account for the enhanced efficacy at tolerated dosages seen with the combinations.

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Termination of Sustained Ventricular Tachycardia by External Noninvasive Pacing

JERRY C. LUCK, MD, BLAIR P. GRUBB, MD, STEPHEN E. ARTMAN, CCVT, ROBERT T. STECKBECK, RN, and MICHAEL L. MARKEL, MD

Cardiac pacing has proven useful in the termination of sustained ventricular tachycardia (VT). In this study, the effectiveness of external noninvasive temporary pacing was compared with traditional endocardial burst ventricular pacing for the termination of sustained and hemodynamically stable VT. In 14 patients, 16 VT morphologies induced by programmed right ventricular extrastimulation were reproducibly terminated by endocardial burst pacing (3 to 9 complexes). VT cycle lengths averaged 392 ± 97 ms (standard deviation) and ranged from 300 to 690 ms. The endocardial burst pacing cycle length used to terminate VT averaged 298 ± 93 ms (range 220 to 600 ms). External burst pacing terminated 14 of 16 VT morphologies (88%). The pacing cycle length used to terminate these 14 VTs averaged 282 ± 44 ms. The number of ventricular captures ranged from 5 to 20 beats. Failure to terminate 2 VT morphologies probably represented a failure of the device to capture the ventricle. Acceleration of VT occurred in 1 patient with burst external noninvasive pacing. These observations suggest that external burst pacing may be an effective means of terminating sustained VT in some patients.

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Sustained ventricular tachycardia (VT) can be terminated by cardiac pacing from either an endocardial or epicardial site.[1-4] Overdrive endocardial burst ventricular pacing has been shown to terminate sustained VT in 60 to 90% of cases.[5,6] A few case reports have documented the use of external (transcutaneous) pacing in the termination of VT.[7-10] To determine the role that external pacing may play in the termination of VT, we compared the effectiveness of external to endocardial burst ventricular pacing for the termination of sustained VT.

Methods

There were 14 patients (3 women and 11 men), mean age 63 ± 9 years (mean ± standard deviation). Thirteen patients had coronary artery disease and 1 had dilated cardiomyopathy. All patients with coronary artery disease had had a myocardial infarction (>2 months before electrophysiologic testing). All were recruited from subjects undergoing routine electrophysiologic testing for sustained VT or ventricular fibrillation. Patients gave informed written consent before electrophysiologic testing. The protocol had been approved by the Clinical Investigation Committee of the University and Hospital.

Only patients with inducible sustained VT using programmed stimulation were candidates. Sustained VT had to be well tolerated and easily terminated on 2 occasions by burst ventricular pacing from an endocardial site to qualify for external pacing. To terminate ventricular tachycardia by both endocardial and external means, only burst ventricular pacing was used. The initial endocardial burst pacing cycle length was 50 to 70 ms less than that of the VT. Endocardial pacing was synchronized and performed at 2 times diastolic threshold for 3 to 10 beats initially. If VT persisted, then the pacing cycle length was reduced by 10- to 20-ms decrements.

For termination of VT by external pacing, we used a Zoll noninvasive temporary pacemaker (ZMI Corp.) modified to allow for tracking of a stimulus from a standard programmable stimulator. The upper rate limit of the standard unit (180 beats/minute) was increased by reducing the refractory period of the device. Asynchronous burst pacing could be performed in the VVT mode.

External burst ventricular pacing was performed after establishing the pacing threshold in sinus rhythm. The threshold for pacing during VT was ini-

From the Department of Medicine, Cardiology Division, The Pennsylvania State University, Hershey, Pennsylvania. Manuscript received August 27, 1987; revised manuscript received October 21, 1987, and accepted October 23.

Address for reprints: Jerry C. Luck, MD, The Milton S. Hershey Medical Center, Department of Medicine, P.O. Box 850, Hershey, Pennsylvania 17033.

tially set at 20 mA above the sinus pacing threshold. The initial pacing cycle length was set at or 20 ms above the endocardial cycle length that terminated the VT. If there was failure to capture consistently at this cycle length, then the output was increased in 20-mA increments until consistent capture was obtained. If VT persisted, the cycle length of pacing was shortened by 10- to 20-ms increments to facilitate ventricular capture and termination of VT (Figure 1). If external pacing was not successful in terminating the ventricular tachycardia, then endocardial pacing or direct current cardioversion was used.

Patients were sedated with midazolam, 4 to 8 mg intravenously in 2 mg divided doses every 5 minutes until somnolence. Both induction and termination of VT were performed with the patients sedated.

Results

In 14 patients, a total of 25 different VT morphologies were induced in the basal state. Only 2 VT morphologies were hemodynamically stable and easily terminated by endocardial burst pacing. All 14 patients then underwent drug testing with an antiarrhythmic agent or agents. Fourteen VT morphologies were induced and reproducibly terminated with endocardial pacing only after the administration of an antiarrhythmic agent. These agents failed to prevent induction of VT but did slow VT rates. These 16 VT morphologies were then tested for termination by external burst pacing (Table I).

For endocardial pacing, the stimulation threshold ranged from 0.3 to 1.0 mA at the right ventricular apex. The current used for endocardial induction and termination of VT was set at twice diastolic pacing threshold with the output set at a minimum of 1.0 mA (range 1.0 to 2.0) The pacing threshold for external pacing during sinus rhythm averaged 76 ± 14 mA. Increasing the current by merely 20 mA for external pacing during VT rarely allowed for consistent ventricular capture during burst pacing. Thus, pacing currents generally required to terminate VT averaged 107 ± 23 mA (range 60 to 140) and were significantly higher than those in sinus rhythm ($p < 0.005$).

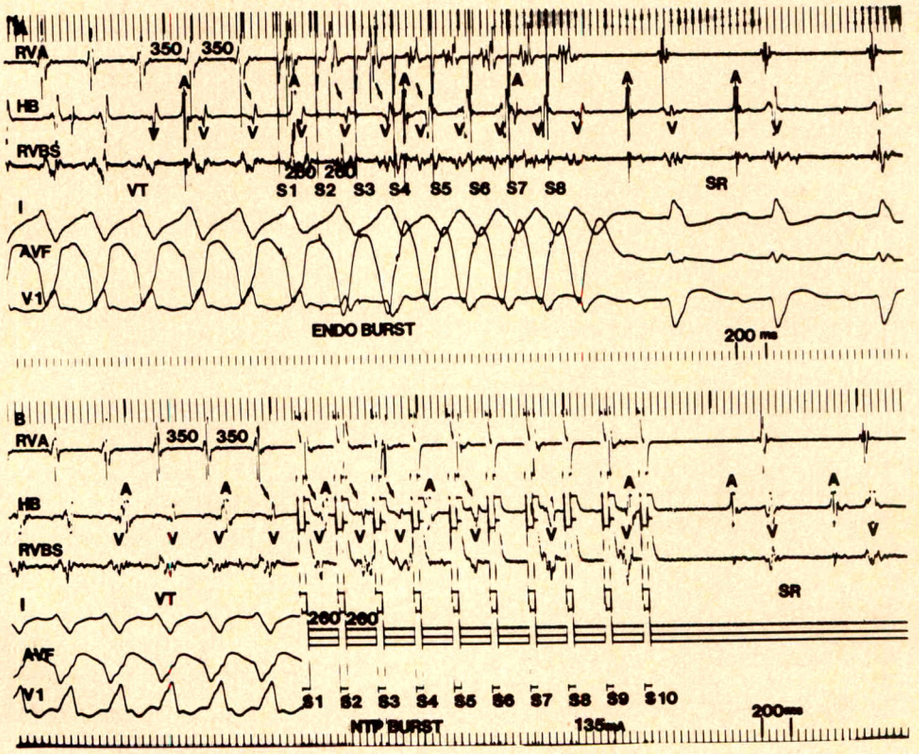

FIGURE 1. ***A*** **(patient no. 2) is an example of ventricular tachycardia (VT) termination by endocardial burst (Endo Burst) ventricular pacing. The intracardiac electrograms (RVA = right ventricular apex; HB = HIS bundle; RVBS = right ventricular basal septum) are recorded simultaneously with surface leads I, aVF, V_1. The VT morphology is one of right bundle branch block at a cycle length of 350 ms. Atrioventricular dissociation is present during both VT and pacing.** ***Arrows*** **indicate the sequence of activation. The apex of the right ventricle is activated before the basal septum (HB, RVBS) during VT. Termination of VT is achieved by burst pacing from the RVA for 8 beats (S1 through S8) at a cycle length of 260 ms. Sinus rhythm (SR) follows. A = atrium; V = ventricle; S = stimulus.** ***B*** **is an example of VT termination in the same patient by external noninvasive temporary pacing (NTP). Intracardiac and surface electrograms are the same as in** ***A*****. The VT morphology and rate are the same. Atrioventricular dissociation is present during both VT and external pacing. With external pacing, VT is terminated and sinus rhythm follows. External pacing at 135 mA allowed for intermittent ventricular capture. S1 fuses with the VT. S2 and S3 capture but S4 fails to capture. S5, S7 and S9 capture the ventricle. Only 6 of 10 stimuli capture the ventricle despite the high current. Activation of the ventricle during external pacing appears to start at the apex and move cephalad (*** ***arrows*** **indicate sequence of activation: RVA to HB, to RVBS electrograms). This suggests that only a small part of the ventricle is activated with external pacing.**

TABLE I Comparison of Endocardial and External Burst Pacing

Pt	Age (yrs), Sex	VT Morph	VT CL (ms)	VT Rate (bpm)	Pacing CL Termination Endo/EXP	Beats for Termination Endo/EXP	EXP-mA Threshold/ Burst
1	43, M	LBBB/NL	340	176	240/240	9/20	80/130
2	52, M	RBBB/RAD	350	171	260/260	7/6	100/135
3	57, F	LBBB/LAD*	320	187	250/240	9/10	81/81
4	58, M	LBBB/LAD	330	181	230/250	8/8	72/90
5	62, M	RBBB/LAD	420	143	360/360	5/5	90/120
6	62, M	RBBB/RAD	310	194	260/260	7/9	75/108
7	63, M(a)	LBBB/RAD	360	167	260/failed	9/—	80/120
	(b)	RBBB/LAD	300	200	220/260	7/7	80/135
8	64, M	RBBB/RAD	380	157	240/240	4/9	84/100
9	65, M	LBBB/LAD*	310	194	250/260	9/11	50/140
10	67, M	RBBB/RAD	380	157	280/260	9/9	56/90
11	69, M	LBBB/LAD	690	87	600/failed	3/—	—/100
12	71, F(a)	RBBB/RAD	460	130	280/300	6/6	89/101
	(b)	LBBB/LAD	410	146	350/350	8/7	60/101
13	76, F	LBBB/LAD	430	129	350/330	7/7	60/60
14	79, M	LBBB/NL	480	125	340/340	3/5	89/109

* Termination without antiarrhythmic agents; all other VTs studied while patients were taking antiarrhythmic agents.

a, b, = 2 different VT morphologies in the same patient; bpm = beats/min; CL = cycle length; Endo = endocardial; EXP = external pacing; EXP-mA = external pacing current strength; LAD = left axis deviation; LBBB = left bundle branch block; NL = normal axis; RAD = right axis deviation; VT = ventricular tachycardia.

The 16 VTs had an average cycle length of 392 ± 97 ms. The endocardial burst pacing cycle length used to terminate VT averaged 298 ± 93 ms. The lowest number of beats terminating VT is listed in Table I.

External burst pacing terminated 14 of 16 VT morphologies (Table I). The average cycle lengths of the 14 VTs was 372 ± 59 ms. The average external pacing cycle length that successfully terminated VT was 282 ± 44 ms. The fewest number of ventricular captures terminating VT is listed in Table I. The cycle lengths and number of beats used by both methods were similar (Table I).

External pacing failed to terminate 2 VTs. In patient 7, VT with a left bundle branch block configuration could not be terminated at current strengths of 120 mA. In this patient, conversion to a different VT morphology with acceleration in the rate occurred with external pacing (Figure 2). This VT terminated spontaneously after about 20 seconds. In the same patient, a VT with right bundle branch block morphology was easily terminated with external pacing at 135 mA. Patient 11 was receiving amiodarone and mexiletine, and his VT was slowed to a cycle length of 690 ms. Endocardial pacing easily terminated his VT with 3 stimuli at a cycle length of 600 ms that was synchronized to the VT beats. However, external burst pacing with current strengths between 60 and 100 mA and cycle lengths of 600 to 430 ms failed to terminate VT. Endocardial electrograms were not available and it was difficult to determine if there was ventricular capture by the external device.

Ventricular activation during external pacing was difficult to ascertain with the present recording apparatus. Intracardiac electrograms helped to determine the activation sequence. Only ventricular capture was seen despite the use of as much as 140 mA in 1 patient.

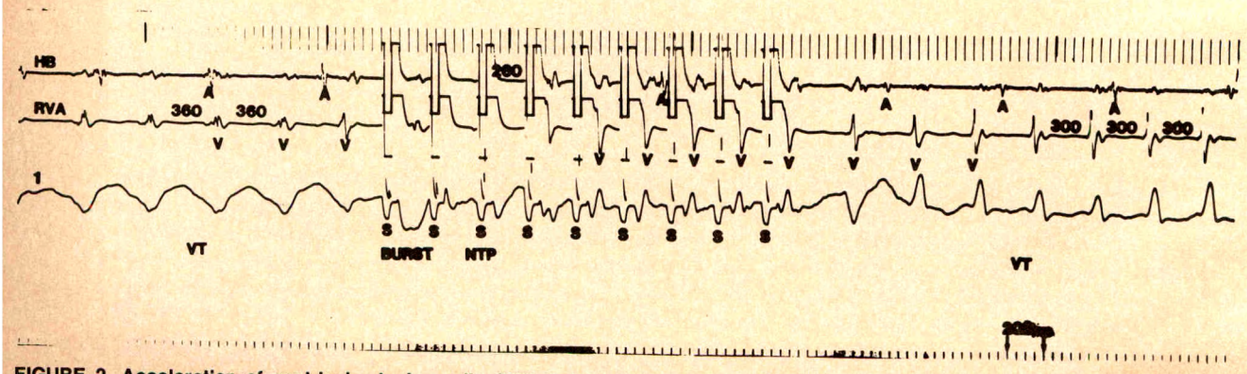

FIGURE 2. Acceleration of ventricular tachycardia (VT) by external noninvasive temporary pacing (NTP) in patient 7. Intracardiac electrograms are recorded simultaneously with lead I. Atrioventricular dissociation is present during both VT and pacing. The VT has a cycle length of 360 ms and is predominantly negative in lead I. Burst external pacing at 260 ms converts the first VT to a second faster VT (cycle length 300 ms). The first 3 stimuli (S) fail to capture the ventricle. Stimuli 4 through 9 consistently capture the ventricle but do not suppress the VT. Abbreviations as in Figure 1.

From some tracings, it appears that external pacing activates the ventricular apex and spreads cephalad (Figure 1).

In order to reduce the muscular discomfort of external pacing, all patients were given 4 to 8 mg of midazolam intravenously before induction and termination of VT with both methods. While in the sedated state, all patients tolerated external pacing well and following the study, no patient recalled the experience as particularly unpleasant. Midazolam produced Cheyne-Stokes respiration in 3 patients but no patient required ventilatory assistance.

Discussion

Termination of sustained VT by pacing techniques is well established.[1-6,11] Our experience with endocardial overdrive burst pacing for termination of VT is similar to that of others,[11] with VT rates >200 beats/min being difficult to terminate. In contrast, 90% of VTs with rates <200 beats/min are terminated by pacing.[5] External noninvasive pacing may also be useful in terminating sustained VT.[7-10] To evaluate the safety and effectiveness of external noninvasive pacing for the termination of sustained VT, we compared it with endocardial burst pacing. We chose endocardial burst pacing because it is an established modality with a success rate of approximately 90%.[5] In addition, it is the pacing technique most easily duplicated by the modified external pacemaker used in this study; our modified Zoll noninvasive temporary pacemaker can deliver a burst of asynchronous stimuli.

Our data show that external noninvasive burst ventricular pacing is quite comparable to endocardial right ventricular burst pacing for the termination of VT. Fourteen of 16 episodes (88%) of sustained, hemodynamically stable VT were terminated by external pacing. The rate of the VTs terminated by external pacing averaged 163 beats/min.

The inability of external noninvasive pacing to terminate some VTs may be due to either a tachycardia unresponsive to pacing or a failure of the device to actually capture the heart.[12,13] In both of our failures, adequate capture was not achieved, probably because higher pacing currents were required. In fact, we found that the external pacing thresholds required to terminate VT were significantly higher than those required to pace in sinus rhythm. It has been previously recognized that increasing the current (mA) for endocardial burst pacing to 10 to 14 mA facilitates capture and VT termination.[14] Our data suggest that high current strengths are equally important in termination of VT with external pacing.

Rapid ventricular pacing can result in acceleration of VT rate or induction of ventricular fibrillation.[6,11] The incidence of acceleration of the VT rate with endocardial burst pacing ranges from 4 to 24%.[5,6,11] Our incidence of acceleration of VT rate with external pace termination was 6% (1 of 16 VT morphologies). As expected, external burst ventricular pacing for VT termination carries much the same risk of acceleration as endocardial burst pacing.

This study has several limitations. It was not a general efficacy study for external pace termination of VT. Our patient population was preselected to allow comparison of 2 pacing modalities. VT rates were slower and allowed for endocardial burst pacing termination. External burst pacing was not used in termination of VTs that were rapid and had failed endocardial termination. The cycle lengths needed to terminate tachycardia were predetermined for external pacing by results of endocardial burst termination. During spontaneous VT, pacing parameters would need to be determined for external pacing. Determining ventricular capture at rapid burst rates is difficult with existing recording equipment because the external stimulus artifact obliterates conventional surface electrocardiographic tracings.

From these preliminary observations it seems reasonable to conclude that external burst ventricular pacing will be an effective means of terminating some forms of VT,. The relative simplicity, safety and reasonably good patient tolerance of the technique make it an attractive potential addition to current methods of antitachycardia pacing. We advise caution, however, because the general clinical utility and safety of external burst ventricular pacing as a primary therapy for VT has yet to be established. Further comparisons with more sophisticated modalities, such as synchronized programmed stimulation and ramp pacing, will be necessary to better define the exact role and limitation of this technique.

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Prognostic Significance of Arrhythmia Inducibility or Noninducibility at Initial Electrophysiologic Study in Survivors of Cardiac Arrest

ROGER A. FREEDMAN, MD, CHARLES D. SWERDLOW, MD, VIVIAN SODERHOLM-DIFATTE, BA, and JAY W. MASON, MD

The value of arrhythmia inducibility or noninducibility at initial electrophysiologic study to predict the likelihood of arrhythmia recurrence was assessed in 150 consecutive survivors of cardiac arrest. Ventricular tachycardia (≥6 beats) or ventricular fibrillation was induced in 113 patients (75%); ventricular arrhythmia could not be induced in 37 patients (25%). During follow-up of a mean of 16 months (range 1 to 72), there were 65 arrhythmia recurrences, 34 of them fatal, in 58 patients. Multivariate regression analysis showed that inducibility at initial study of ventricular tachycardia or ventricular fibrillation was an independent predictor of total arrhythmia recurrence ($p < 0.0001$) and fatal arrhythmia recurrence ($p = 0.02$). At 1 year, 25 ± 5% of patients with an inducible arrhythmia had a fatal arrhythmia recurrence compared with only 4 ± 4% of patients without ($p = 0.003$). The nature of the inducible arrhythmia had no additional predictive value. Inducibility or noninducibility of ventricular arrhythmias at initial electrophysiologic study is a powerful, independent predictor of subsequent arrhythmia recurrence in survivors of cardiac arrest. Patients without inducible arrhythmias have a low frequency of fatal arrhythmia recurrence.

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The incidence of recurrent cardiac arrest in patients who have been successfully hospitalized and discharged following a first episode of cardiac arrest is 10 to 25% in the first year and approximately 5% a year subsequently.[1,2] All medical and surgical antiarrhythmic therapy advocated in survivors of cardiac arrest have substantial morbidity and the potential for worsening arrhythmias.[3–5] Prospective identification of patients at greater or lower risk for recurrence could determine the need to institute such therapy.

Ventricular tachycardia (VT) or ventricular fibrillation (VF) can be induced during initial electrophysiologic study (when the patient is receiving no antiarrhythmic drug) in most survivors of cardiac arrest.[6–13] Some previous studies[6,7,11,12] have suggested that patients in whom no arrhythmias are inducible are at low risk for recurrent cardiac arrest, while others have suggested no risk advantage in this group.[9,10,13] Several of these prior studies included small numbers of patients and most did not use actuarial methods to analyze recurrence. We used actuarial methods to determine the prognosis in 37 survivors of cardiac arrest without inducible arrhythmias, and compared their prognosis with that of 113 concurrent survivors of cardiac arrest who had inducible arrhythmias.

From the Cardiology Division, Stanford University Medical Center, Stanford, California, and the Cardiology Division, University of Utah Medical Center, Salt Lake City, Utah. Manuscript received September 3, 1987; revised manuscript received October 21, 1987, and accepted October 23.

Address for reprints: Roger A. Freedman, MD, Cardiology Division, University of Utah Medical Center, 50 North Medical Drive, Salt Lake City, Utah 84132.

Methods

Patients: The patients are 150 consecutive survivors of cardiac arrest who underwent a uniform stimulation protocol at initial (i.e., without antiarrhythmic drug) electrophysiologic study. A patient was considered to have survived a cardiac arrest if he or she had a witnessed, sudden loss of consciousness, was pulseless and apneic and required external direct current cardioversion. Patients whose arrest occurred within 7 days of an acute myocardial infarction or cardiac surgery were excluded. Of the patients with myocardial

infarction, 90% had cardiac arrest >30 days after onset of the infarct.

Electrophysiologic study: All patients underwent electrophysiologic study after antiarrhythmic drugs had been withheld for at least 5 drug half-lives. Our ventricular arrhythmia induction protocol has been described previously.[14] It included rapid atrial and ventricular pacing, and up to 3 right ventricular extrastimuli delivered during sinus and ventricular-paced rhythm at 4 basic drive cycle lengths (400 to 600 ms). Ventricular stimulation was initially performed at the right ventricular apex, but it was repeated at a second right ventricular site if an endpoint (discussed next) was not met during stimulation at the apex. Left ventricular stimulation and isoproterenol infusion were not used to induce arrhythmias in these patients. If the patient had had documented, spontaneous, sustained monomorphic VT, the endpoint of the study was induction of 2 sustained monomorphic VT or completion of the stimulation protocol. In those without documented, spontaneous, sustained monomorphic VT, the endpoint of the study was the induction of 2 sustained VT or VF or completion of the protocol.

Induced VT was considered sustained if its duration was at least 15 seconds, and nonsustained if its duration was between 6 beats and 15 seconds. Patients were considered to have no inducible arrhythmias if <6 repetitive beats were reproducibly induced during the stimulation protocol. All episodes of polymorphic VT were either nonsustained or degenerated into VF within 15 seconds; hence all induced arrhythmias could be classified as sustained monomorphic VT, nonsustained VT or VF.

Therapy: In patients with inducible arrhythmias, attempts were made to identify a drug effective in preventing arrhythmia induction, using previously described criteria.[14] If an acutely effective drug was identified and was well tolerated, the patient was discharged receiving it. In patients in whom no acutely effective drug could be identified and in patients without arrhythmias inducible at initial study, therapy was chosen on an individual basis.

Follow-up: Patients were followed for a mean of 16 months (range 1 to 72) after initial electrophysiologic study. Patients or referring physicians were contacted at least every 3 months during follow-up to determine patient status. Follow-up ended on the date of the patient's death or cardiac transplantation, when no information was available on the patient's status (1 patient), or at the end of the study.

During follow-up a witnessed death was classified as sudden if it occurred within 1 hour of onset of symptoms, and an unwitnessed death was classified as sudden unless there was evidence of preceding circulatory failure.[15] All other deaths were classified as nonsudden. A sustained arrhythmia recurrence was diagnosed if sustained VT or VF was documented electrocardiographically, if the patient had syncope without other obvious cause or, in patients with implanted automatic defibrillators, if there was a shock not caused by sinus or supraventricular tachycardia or by malfunction of the device.

TABLE I Comparison of 37 Patients Without Inducible Arrhythmias With 113 Concurrent Patients With Inducible Arrhythmias

	Without Induced Arrhythmias	With Induced Arrhythmias	p Value
Age (yrs)	53 ± 17	56 ± 14	0.3
Male gender (%)	13 (35)	98 (87)	<0.0001
Structural heart disease			
Coronary artery disease* (%)	14 (38)	87 (77)	
Prior MI (%)	7 (19)	85 (75)	
LV aneurysm (%)	4 (11)	53 (47)	
Idiopathic cardiomyopathy (%)	16 (43)	20 (18)	0.0001
Valvular disease (%)	0 (0)	1 (1)	
None (%)	7 (19)	5 (4)	
LV ejection fraction†	45 ± 18	35 ± 14	0.02

* History of myocardial infarction or angina pectoris, or ≥70% stenosis of a coronary artery.

† Determined in 113 patients by either radionuclide or contrast ventriculography.

LV = left ventricular; MI = myocardial infarction.

Statistics: Continuous data are presented as mean ± 1 standard deviation. Student's *t* test statistic or the chi-square statistic was used to compare groups of patients. Actuarial survival estimates were by Kaplan-Meier method, and are expressed as probability ± standard error and compared using the Wilcoxon statistic.[16] Patients were censored at the time of nonsudden death or last follow-up. Multivariate regression analysis used stepwise Cox proportional-hazard model and the improvement chi-square statistic.[17]

Results

Electrophysiologic study: Sustained, monomorphic VT was induced in 82 patients (55%), VF in 23 (15%), nonsustained VT in 8 (5%) and no arrhythmia in 37 (25%). Clinical characteristics of the 37 patients without inducible arrhythmia are compared with those of the 113 patients with inducible arrhythmia in Table I.

Therapy: Therapy at discharge in the 37 patients without inducible arrhythmias was an antiarrhythmic drug in 19 (51%), automatic defibrillator in 7 (19%) and coronary artery bypass surgery in 3 (8%). There was no therapy in 8 (22%).

Of the 113 patients with inducible arrhythmias, 10 died and 2 underwent cardiac transplantation before hospital discharge. Therapy at discharge in the remaining 101 patients was an antiarrhythmic drug in 49 (49%), automatic defibrillator in 33 (33%), surgical myocardial ablation in 12 (12%), coronary artery bypass surgery in 4 (4%) and 3 patients (3%) did not receive therapy. Of the 49 patients with inducible arrhythmias who were discharged receiving an antiarrhythmic drug, the drug was found effective by serial electrophysiologic study in 13, ineffective in 11 and not tested in 25.

Arrhythmia recurrences: The actuarial incidences of fatal recurrence (sudden death) at 1 and 2 years were 20 ± 4% and 27 ± 5%, respectively. The actuarial

TABLE II Raw Arrhythmia Recurrence Data in Patients With and Without Inducible Arrhythmias During Mean Follow-Up of 16 Months

	Sudden Death	Nonfatal Arrhythmia	No Arrhythmia Recurrence
Inducible arrhythmia (n = 113)	32 (28%)	28* (25%)	60 (53%)
No inducible arrhythmia (n = 37)	2 (5%)	3 (8%)	32 (87%)

* Includes 7 patients who died suddenly during subsequent follow-up.

incidences of total recurrence (sudden death or sustained arrhythmia) at 1 and 2 years were 34 ± 4% and 41 ± 5%, respectively.

Arrhythmia recurrences for patients with and without arrhythmias induced at initial electrophysiologic study are listed in Table II. Recurrences were much less frequent in patients without inducible arrhythmias than in those with inducible arrhythmias. This difference is confirmed using actuarial methods (Figure 1). At 1 year, the risks of fatal and total arrhythmia recurrences were 6.3- and 2.9-fold greater, respectively, in patients with inducible arrhythmias than in those without.

Compared with patients without inducible arrhythmias, the increased relative risk of arrhythmia recurrence in patients with inducible arrhythmias was present regardless of the type of ventricular arrhythmia induced. Recurrence rates did not differ significantly between those whose induced arrhythmia was sustained monomorphic VT, VF or nonsustained VT.

Other univariate correlates of arrhythmia recurrence were New York Heart Association functional class, presence of coronary artery disease, age and ejection fraction.

By stepwise Cox multivariate regression survival analysis, arrhythmia inducibility at initial electrophysiologic study was an independent predictor of both total ($p < 0.0001$) and fatal ($p = 0.02$) arrhythmia recurrences. Other independent predictors were history of prior myocardial infarction and New York Heart Association functional class. Variables without significant independent predictive value for either fatal or total recurrences were age, gender, coronary artery disease and left ventricular aneurysm. Left ventricular ejection fraction was excluded from these analyses because it was not determined in all patients.

The wide variety of therapies used in these patients, and the fact that therapy was not prescribed in a controlled fashion, hinder analysis of the overall effect of therapy on arrhythmia recurrence. However, several observations are of interest. As expected, among patients with inducible arrhythmias at initial study, those receiving antiarrhythmic drugs predicted effective at follow-up study had fewer recurrences (1 year fatal recurrence rate is 25%) than those receiving drugs predicted ineffective (1 year fatal recurrence rate is 55%). However, patients without inducible arrhythmias at initial electrophysiologic study had even fewer recurrences (1 year fatal recurrence rate is 4%) than those with inducible arrhythmias receiving drugs predicted effective. In particular, the 12 patients without inducible arrhythmias (including 4 who received an implanted defibrillator) who were discharged receiving no antiarrhythmic drugs had no arrhythmia recurrences, fatal or nonfatal, through 1 year.

Discussion

Relations of arrhythmia inducibility to prognosis: The principal finding of this study is that arrhythmia inducibility at initial electrophysiologic study is a powerful, independent predictor of outcome in patients resuscitated from cardiac arrest. Several previous studies have assessed the correlation between arrhythmia inducibility and subsequent sudden death or arrhythmia recurrence in survivors of cardiac arrest. Ruskin et al[11] found no deaths in 14 survivors of cardiac arrest who did not have inducible VT or VF and were followed for 15 months. Morady et al[7] found no recurrences in 11 such patients followed for 19 months. However, other investigators have found high recurrence rates in survivors of cardiac arrest without inducible VT or VF. Roy et al[9] reported 10 sudden

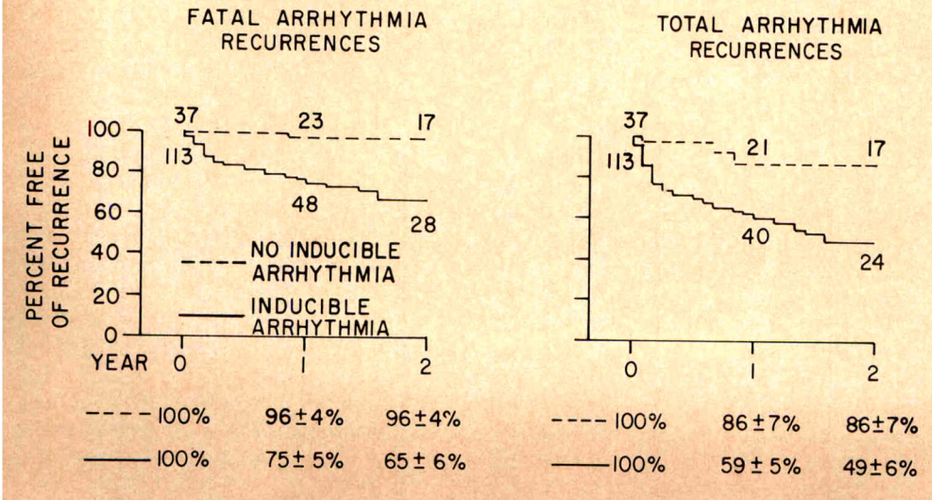

FIGURE 1. Actuarial curves for fatal (*left*) and total (*right*) arrhythmia recurrence stratified by presence or absence of inducible arrhythmias at initial electrophysiologic study. The numbers next to the curves indicate number of patients at risk. The numbers below the graphs indicate probability of freedom from recurrence ± standard error. The differences between curves for fatal arrhythmia recurrence are significant ($p = 0.003$). The differences between curves for total arrhythmia recurrence are significant ($p = 0.0006$).

deaths in 36 patients followed for 20 months, Henthorn et al[10] reported 7 sudden deaths and 6 nonfatal VT recurrences in 23 patients followed for 15 months and Eldar et al[13] reported 3 sudden deaths and 5 nonfatal recurrences in 33 patients followed for 27 months.

These previous studies have certain limitations. First, only 1 of them[13] used actuarial methods to assess the predictive value of initial arrhythmia inducibility. Second, a concurrent comparison group of survivors of cardiac arrest with inducible VT or VF was not always included.[10] Third, among those that found arrhythmia inducibility to be a significant prognostic factor, none used multivariate analysis to determine if its effect was independent of the effects of other variables.

In the present study, using actuarial analysis, we found that presence or absence of inducible VT or VF at initial electrophysiologic study was a strong univariate predictor of both fatal ($p = 0.003$) and total ($p = 0.0006$) arrhythmia recurrence. Further, the predictive value of the initial electrophysiologic study was independent of other predictors of arrhythmia recurrence. These findings contrast with those recently reported by Eldar et al,[13] who also used actuarial analysis but found no difference in prognosis between patients with and without arrhythmias inducible at initial electrophysiologic study. One possible explanation for the disparity is the much higher incidence of recurrent arrhythmias in the present study compared with that of Eldar et al.[13] For instance, in patients with inducible arrhythmias, the 1 year incidence of fatal arrhythmia recurrence was 8.5% in Eldar et al[13] versus 25% in the present study. The lower incidence of arrhythmia recurrences in the prior study may have limited its power in discerning a difference in prognosis between patients with and without inducible arrhythmias. Further, the disparity in recurrence rates suggests a difference in patient population.

Arrhythmia inducibility has been shown to be a predictor of prognosis in other patient populations. Denniss et al[18] have shown that after myocardial infarction, patients with inducible VT had a greater incidence of ventricular tachyarrhythmias and death than patients without inducible arrhythmias. In patients with spontaneous nonsustained VT, Gomes,[19] Buxton[20] and their co-workers have shown that patients with inducible arrhythmias were more likely to suffer sustained VT or sudden death. Thus, the prognostic implication of arrhythmia inducibility in our population of cardiac arrest survivors is paralleled by similar findings in other patient groups.

Significance of inducing nonsustained ventricular tachycardia or ventricular fibrillation: Some investigators[21,22] have questioned the significance of inducing nonsustained VT or VF, because these arrhythmias may be induced in some patients without spontaneous arrhythmias. In the present study, patients with nonsustained VT or VF induced at initial electrophysiologic study had significantly higher arrhythmia recurrence rates than patients with no inducible arrhythmia. These results suggest that in survivors of cardiac arrest, inducibility of nonsustained VT or VF may not be a nonspecific response.

Limitations: A weakness of this study is that therapy was not prescribed in a controlled fashion, and a wide range of therapy was used in both patients with and without inducible arrhythmias. Specifically, the influence of therapy on the natural history of our patients without inducible arrhythmias is not known. It is noteworthy that, among the patients without inducible arrhythmias, those who received no drug therapy had fewer recurrences than those who did receive antiarrhythmic drugs. This comparison is limited by the fact that therapy was not assigned in a controlled or randomized fashion.

A second limitation of this study is that ambulatory electrocardiographic monitoring was not routinely performed in the study population. Prior studies have yielded conflicting results on whether the frequency and complexity of ventricular premature beats are predictive of recurrent cardiac arrest.[23–25]

Implications: Why is arrhythmia inducibility at initial electrophysiologic study an independent predictor of arrhythmia recurrence in survivors of cardiac arrest? One possible explanation is that transient but not frequently recurrent metabolic disturbances, such as electrolyte abnormalities or ischemia, play a larger role in patients without inducible arrhythmias than in those with inducible arrhythmias. This hypothesis was not examined in the present study.

Ideally, only those survivors of sudden death at high risk for arrhythmia recurrence should receive potentially toxic antiarrhythmic drugs or major surgical procedures. In this study, arrhythmia inducibility at initial electrophysiologic study was a powerful predictor of arrhythmia recurrence. Patients with inducible arrhythmias had a 25% probability of fatal recurrence at 1 year, and aggressive therapy is indicated in this group. On the other hand, patients without inducible arrhythmias had only a 4% probability of fatal recurrence at 2 years, and the appropriateness of aggressive therapy in this group is therefore questionable.

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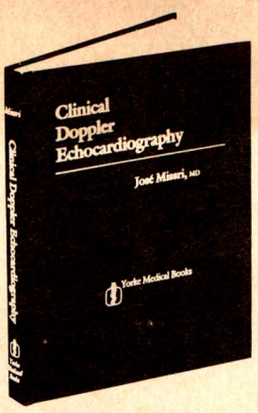

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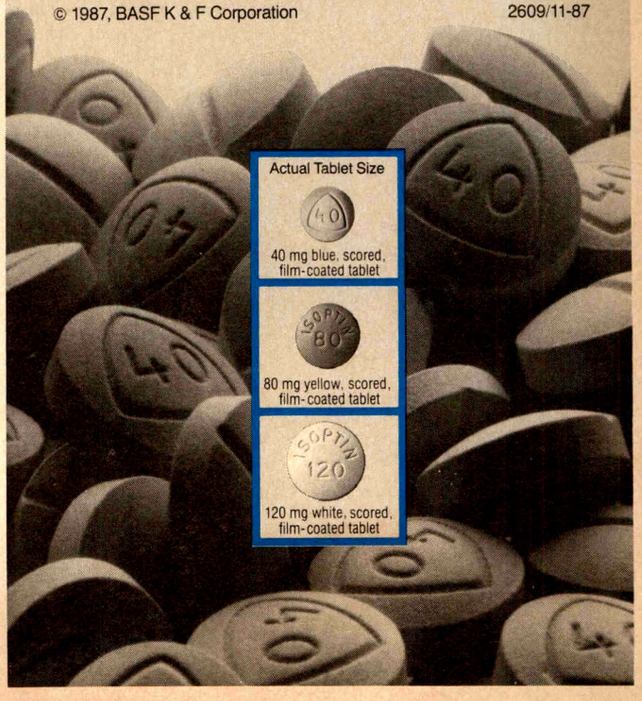

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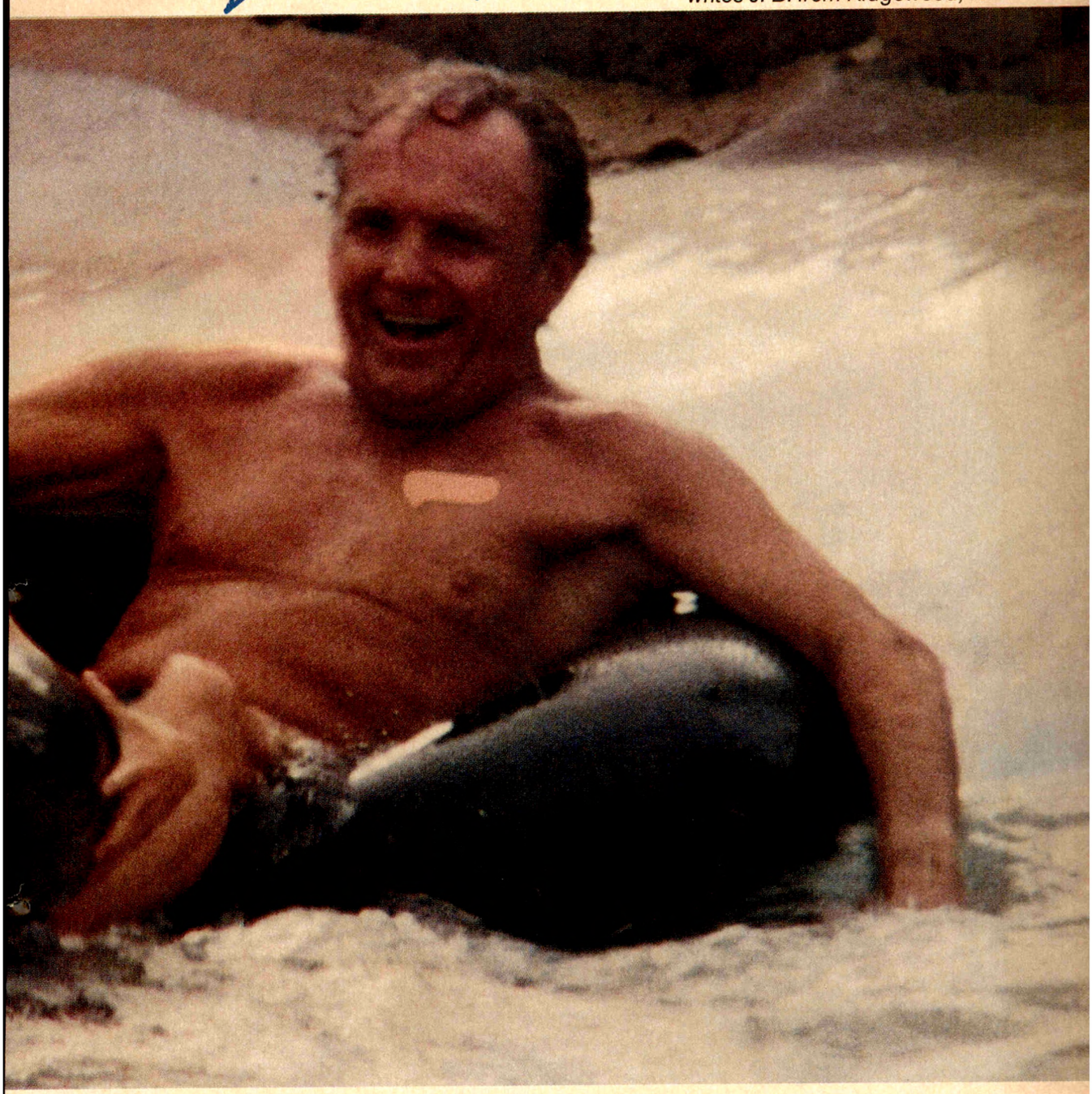

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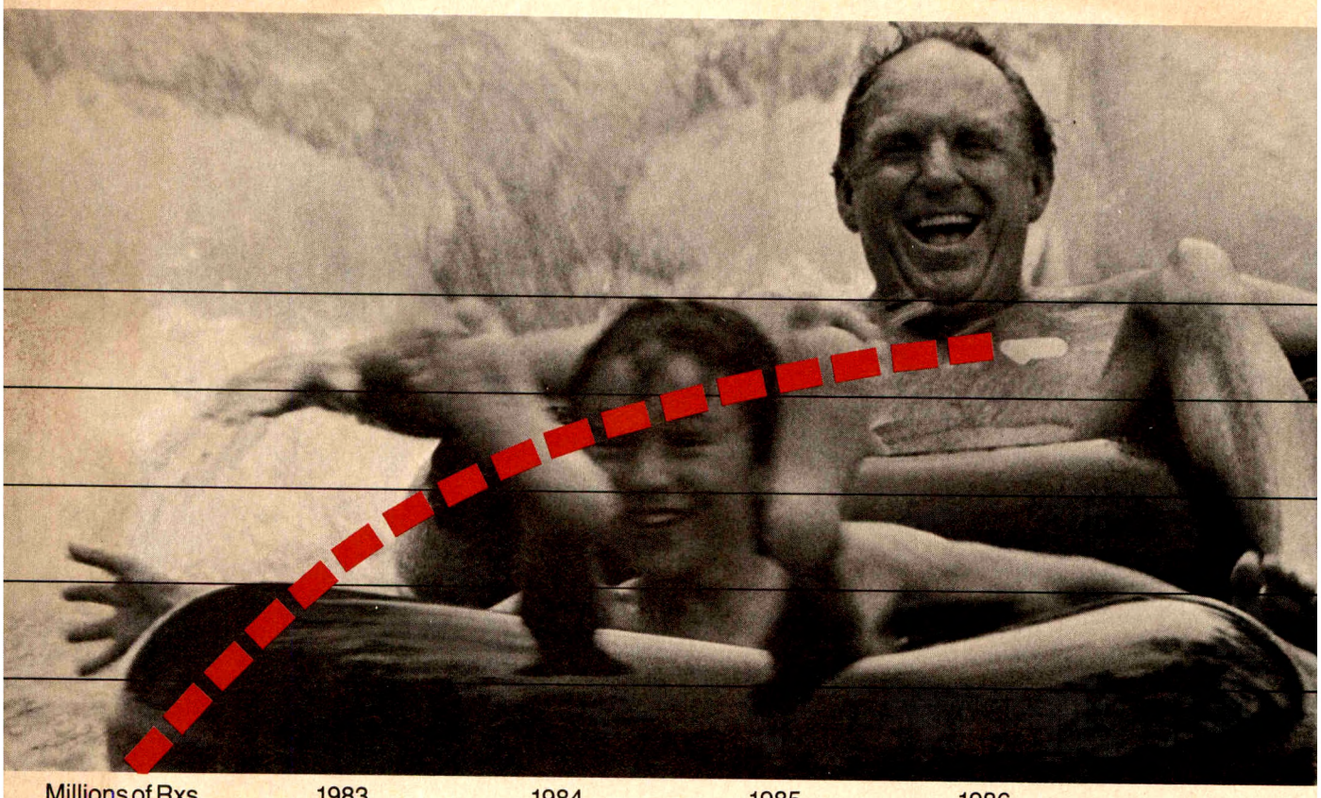

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INDICATIONS AND USAGE
This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS
Intolerance of organic nitrate drugs, marked anemia, increased intraocular pressure or increased intracranial pressure.

WARNINGS
In patients with acute myocardial infarction or congestive heart failure, Transderm-Nitro system should be used under careful clinical and/or hemodynamic monitoring.
In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.
Transdermal nitroglycerin systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

PRECAUTIONS
Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.
Transderm-Nitro system is not intended for immediate relief of anginal attacks. For this purpose occasional use of the sublingual preparations may be necessary.

ADVERSE REACTIONS
Transient headaches are the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Transderm-Nitro therapy is continued. When such headaches are unresponsive to treatment, the nitroglycerin dosage should be reduced or use of the product discontinued.
Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea and vomiting. These symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist the dose should be reduced or use of the product discontinued. In some patients, dermatitis may occur.

DOSAGE AND ADMINISTRATION
Therapy should be initiated with application of one Transderm-Nitro 5 mg/24 hr system to the desired area of skin. Many patients prefer the chest; if hair is likely to interfere with system adhesion or removal, it can be clipped prior to placement of the system. Each system is designed to remain in place for 24 hours, and each successive application should be to a different skin area.
Transderm-Nitro system should not be applied to the distal parts of the extremities.
The usual dosage is one Transderm-Nitro 5 mg/24 hr system. Some patients, however, may require the Transderm-Nitro 10 mg/24 hr system. If a single Transderm-Nitro 5 mg/24 hr system fails to provide adequate clinical response, the patient should be instructed to remove it and apply either two Transderm-Nitro 5 mg/24 hr systems or one Transderm-Nitro 10 mg/24 hr system. More systems may be added as indicated by continued careful monitoring of clinical response. The Transderm-Nitro 2.5 mg/24 hr system is useful principally for decreasing the dosage gradually, though it may provide adequate therapy for some patients when used alone. The optimal dosage should be selected based upon the clinical response, side effects, and the effects of therapy upon blood pressure. The greatest attainable decrease in resting blood pressure that is not associated with clinical symptoms of hypotension especially during orthostasis indicates the optimal dosage. To decrease adverse reactions, the size and/or number of systems should be tailored to the individual patient's needs.
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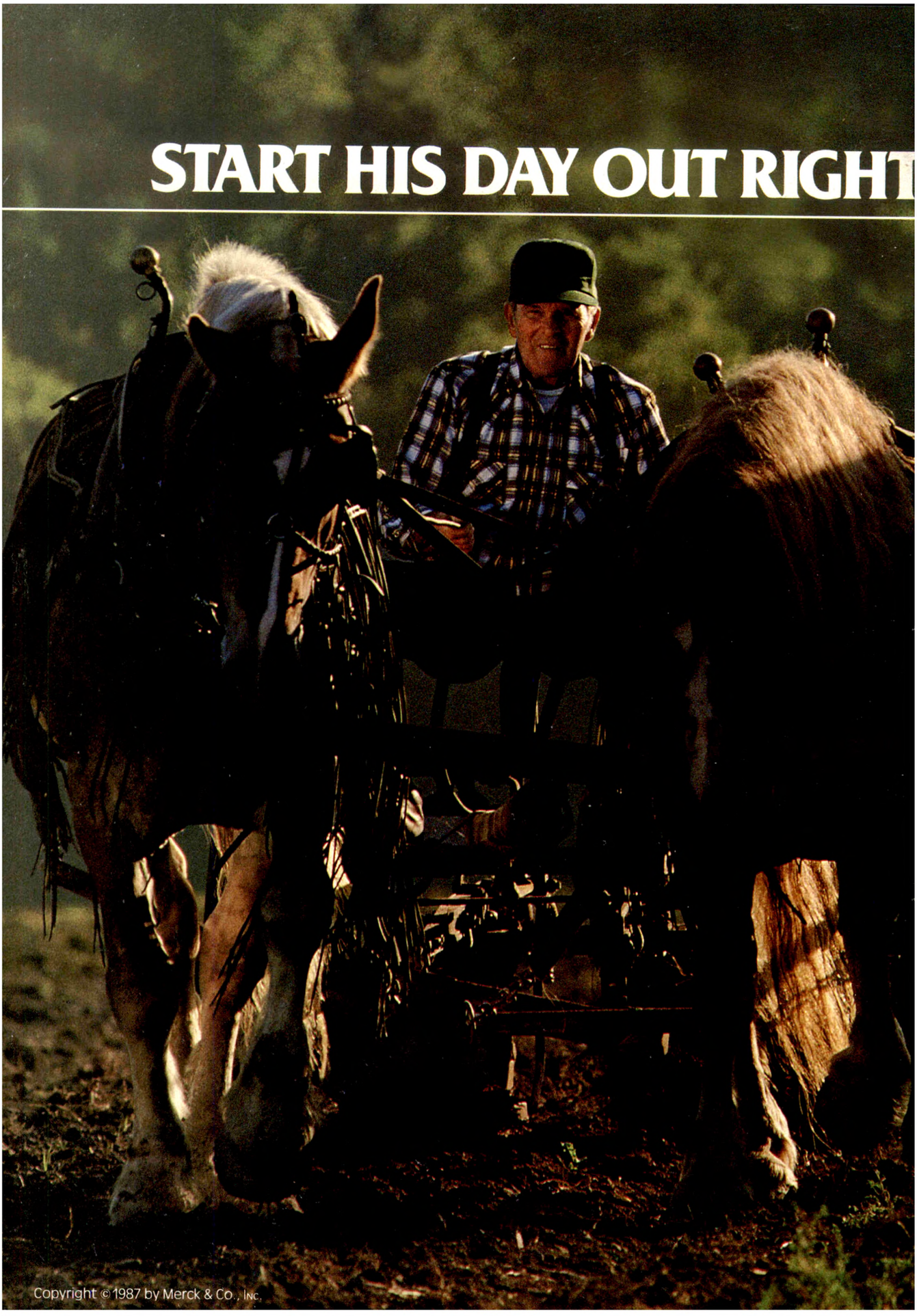

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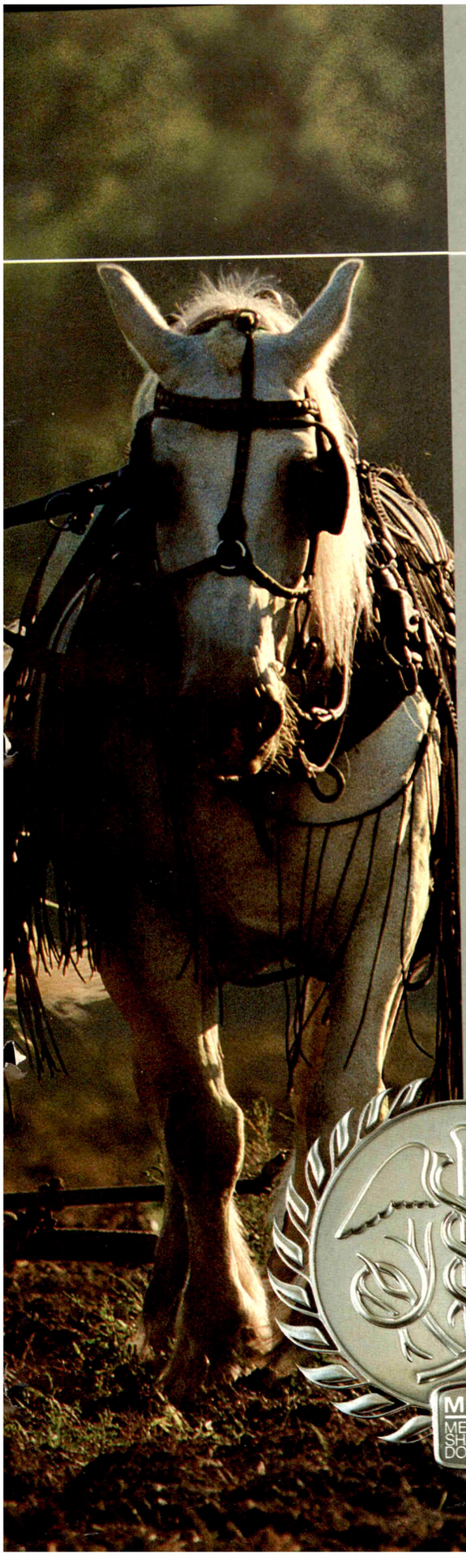

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VASOTEC is contraindicated in patients who are hypersensitive to this product.

Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with angiotensin-converting-enzyme (ACE) inhibitors, including VASOTEC (0.2% of patients treated with VASOTEC in clinical trials). In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.**

Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. In using VASOTEC, consideration should be given to the fact that another ACE inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and the available data are insufficient to show that VASOTEC does not have a similar risk.

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Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another ACE inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of VASOTEC and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION in complete Prescribing Information.)

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia. (See *Drug Interactions*.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least one hour after the initial dose. (See WARNINGS and DOSAGE AND ADMINISTRATION in complete Prescribing Information.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC® (Enalapril Maleate, MSD) has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC may attenuate potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Pregnancy--Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

There are no adequate and well-controlled studies in pregnant women. VASOTEC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2677 patients.

The most frequent clinical adverse experiences in controlled trials were: headache (4.8%), dizziness (4.6%), and fatigue (2.8%). For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 40 mg. The overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.6%), rash (1.5%), hypotension (1.4%), cough (1.3%), nausea (1.3%), and orthostatic effects (1.3%).

Clinical adverse experiences occurring in 0.5% to 1.0% of patients in the controlled trials or since the drug was marketed include:

Cardiovascular: Syncope, orthostatic hypotension, palpitations, chest pain.

Nervous System: Insomnia, nervousness, paresthesia, somnolence.

Gastrointestinal System: Abdominal pain, vomiting, dyspepsia.

Renal: Renal dysfunction, renal failure, oliguria. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION in complete Prescribing Information.)

Other: Dyspnea, muscle cramps, hyperhidrosis, impotence, pruritus, asthenia.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension and other orthostatic effects) was reported in 2.3% of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. (See WARNINGS.)

Clinical Laboratory Test Findings:

Hyperkalemia: (See PRECAUTIONS.)

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Dosage and Administration: In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg (break the 5-mg tablet) should be used under medical supervision for at least one hour to determine whether excess hypotension will occur. (See WARNINGS and PRECAUTIONS, *Drug Interactions.)*

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily. For dialysis patients, the initial dose and the dose on dialysis days is 2.5 mg/day. Dosage on nondialysis days should be adjusted depending on blood pressure response.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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Dual Balloon Technique for Valvuloplasty of Aortic Stenosis in Adults

JEFFREY M. ISNER, MD, DEEB N. SALEM, MD, MARK R. DESNOYERS, MD, CONSTANCE D. FIELDS, MD, KIMBERLY R. HALABURKA, BS, GERALYN A. SLOVENKAI, BS, THOMAS J. HOUGEN, MD, ERIC J. EICHHORN, MD, and KENNETH ROSENFIELD, MD

A dual balloon technique was studied in 16 patients with aortic stenosis in whom results with a single balloon (up to 20 mm, 5.5 cm or 25 mm, 3.0 cm in diameter and length, respectively) were judged to be suboptimal. Dual balloon valvulopasty was performed using 2 balloons advanced and inflated simultaneously across the stenotic aortic valve orifice. For the group as a whole, the average peak transvalvular gradient was reduced from 79 ± 8 to 57 ± 7 mm Hg (mean ± standard error) using a single balloon ($p < 0.0005$), and reduced further to 36 ± 4 mm Hg using dual balloons ($p < 0.0005$ compared with single balloon results). Similarly, calculated aortic valve orifice area was increased from 0.45 ± 0.04 to 0.57 ± 0.05 cm^2 using a single balloon ($p < 0.0005$), and further increased to 0.77 ± 0.06 cm^2 using dual balloons ($p < 0.0005$). Dual balloon dilation caused no complications directly attributable to the use of 2 balloons, including no exacerbation of aortic regurgitation. These results suggest that dual balloon valvuloplasty is safe and efficacious in selected patients with aortic stenosis.

(Am J Cardiol 1988;61:583–589)

Pioneering work by Cribier et al[1,2] in France and McKay et al[3] in the U.S. established the fact that balloon valvuloplasty could accomplish hemodynamic and clinical palliation in most elderly patients with aortic stenosis (AS). Findings reported in these early and other subsequent[4,5] investigations, however, have indicated that when balloon valvuloplasty is performed using 1 or a series of single balloon catheters, the improvement in calculated aortic valve area achieved after valvuloplasty is often modest. Further, preliminary follow-up data recorded noninvasively using Doppler echocardiography or invasively during repeat cardiac catheterization suggests that restenosis may develop in ≥20% of patients followed for ≥6 months after a successful valvuloplasty.[6–8] Accordingly, a number of modifications in the instrumentation and technique used for aortic balloon valvuloplasty have been proposed to augment both the magnitude and duration of acute hemodynamic improvement.[9] We describe results of 1 such technical modification, simultaneous inflation of 2 balloons in 16 patients in whom results obtained using a single balloon were judged to be suboptimal.

From the Departments of Medicine (Cardiology), Pathology and Pediatrics (Cardiology), New England Medical Center/Tufts University School of Medicine, Boston, Massachusetts. This study was supported in part by grant HL 32747-01 and contract NO1-HC55010 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland, and the Eleanor Naylor Dana Charitable Trust, New York, New York. Drs. Fields and Eichhorn were Research Fellows of the American Heart Association's Massachusetts Affiliate during this study. Manuscript received September 3, 1987; revised manuscript received and accepted October 28, 1987.

Dr. Eichhorn's present address: Department of Medicine (Cardiology), Veteran's Administration Hospital, Dallas, Texas.

Address for reprints: Jeffrey M. Isner, MD, Box 70, New England Medical Center, 171 Harrison Avenue, Boston, Massachusetts 02111.

Methods

Patients: The patients selected for dual balloon valvuloplasty constitute a subset of 16 patients (30%) from a total of 51 patients in whom aortic balloon valvuloplasty was performed at our institution during the past

15 months. Patients were judged to be candidates for balloon valvuloplasty in general if a previous cardiac catheterization (or in some cases Doppler echocardiographic examination) documented critical AS and no more than 2+/4+ aortic regurgitation; the patient, because of age or accompanying medical disorders, was considered either noneligible or high risk for aortic valve replacement; or the patient was an operative candidate but refused to undergo surgery. Among 51 such patients, 16 were selected for dual balloon valvuloplasty because the results obtained using 1 or a series of single balloons were judged to be suboptimal; suboptimal was defined as a calculated aortic valve area <0.50 cm^2, a residual transvalvular gradient >35 mm Hg or both. In addition, several patients who fulfilled these criteria were further excluded from consideration for dual balloon valvuloplasty when it was judged that certain technical factors (e.g., severe peripheral vascular disease, small body habitus) might make the dual balloon technique excessively hazardous. Each patient gave informed consent in accordance with a protocol approved by the Institutional Human Investigations Review Committee.

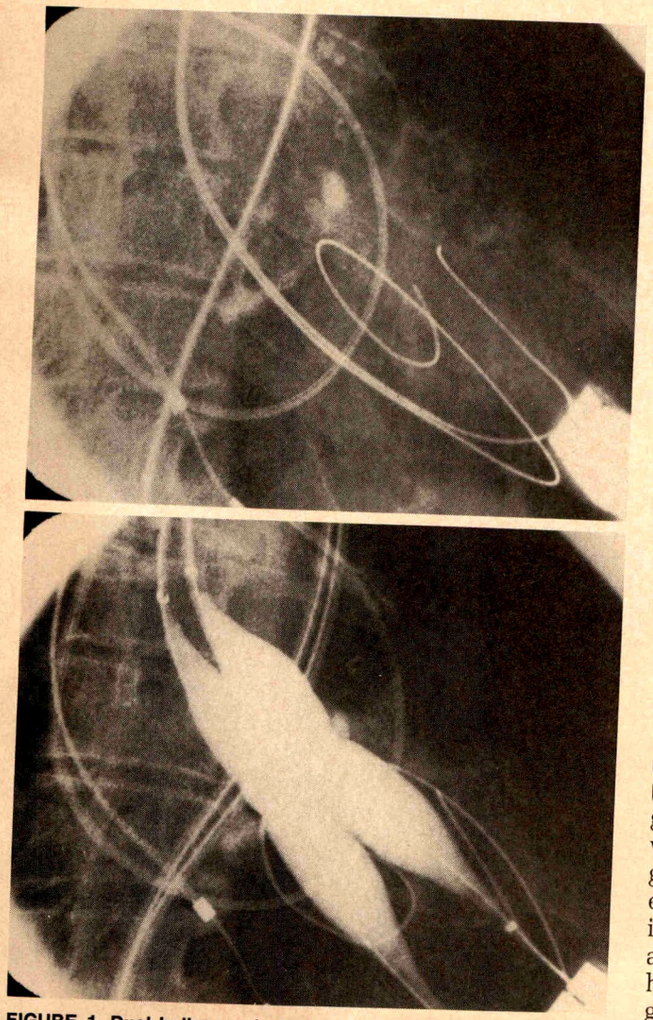

FIGURE 1. Dual balloon valvuloplasty in patient 6 (Table I). *Top*, exchange wires in place across aortic valve. *Bottom*, at full inflation of two 18 mm, 5.5 cm balloons, a "waist" persists at the (heavily calcified) valvular level.

Technique of single balloon valvuloplasty: All patients first underwent balloon valvuloplasty performed with 1 or a series of single balloons as described previously.[4] Briefly, under local lidocaine anesthesia, a small cutdown was performed to expose the right or left common femoral, superficial femoral and profunda femoris arteries. The introducer sheath and guidewire were then introduced through a small scalpel incision directly into the common femoral artery, at which time a bolus of 5,000 to 10,000 U of heparin was administered intravenously. During catheter exchanges not involving the introducer sheath, hemostasis was maintained directly with umbilical tapes proximal and distal to the arterial entry site, and digital compression of the entry site. Small amounts of local bleeding were managed with vacuum suction.

Balloon valvuloplasty was performed using a 9Fr catheter (Mansfield Scientific) with a balloon constructed of polyethylene. The balloon was 15, 18, 20 or 25 mm in diameter and 3.0 or 5.5 cm in length. In most patients, single balloon valvuloplasty was performed using 1, rather than a series, of single balloons and this single balloon was typically 20 mm in diameter and 5.5 cm in length. Likewise, attempts at single balloon valvuloplasty were typically discontinued if an optimal result was not achieved with the 20 mm, 5.5 cm balloon, although in a few of the earlier patients, additional attempts were made using a 25 mm, 3.0 cm balloon. Up to 3 dilations, each 10 to 20 seconds in duration, were performed with each single balloon.

Balloon catheters were introduced directly into the arteriotomy via a 260 cm, 0.038 inch exchange wire (Cook), the distal tip of which was fashioned into an exaggerated "J". After each series of dilations with a single balloon catheter was completed, it was exchanged for an 8FR A-2 multipurpose or 8Fr pigtail catheter (Cordis); the latter was introduced along with a 12Fr introducer sheath (Universal Medical Instruments) to assist hemostasis during hemodynamic assessment.

Technique of dual balloon valvuloplasty: The 260 cm "J"-tipped exchange wire was reintroduced through the diagnostic catheter, which was then removed (Figure 1). A 9Fr angioplasty guide catheter (Schneider-Shiley) or an 8Fr double lumen catheter (Mansfield), which can accommodate two 0.038 inch guidewires, was then introduced over the exchange wire into the left ventricle. A second 260 cm "J"-tipped guidewire was then advanced through the guide catheter into the left ventricle. The guide catheter and introducer sheath were then removed. Because initial applications of the dual balloon technique produced hypotension and bradycardia that appeared to be vagally mediated at the time of dual balloon inflation, subsequent patients routinely received atropine sulfate, 0.8 mg, intravenously at this point. Two new balloon catheters were then introduced in tandem fashion via the exchange wires, up to the level of the dia-

phragm. At this point, any small air bubbles were reevacuated from the syringes used to inflate the balloon (the balloons were otherwise filled with a 2:1 mixture of saline and meglumine diatrizoate). The balloons were then advanced together into the ascending aorta and across the aortic valve into the left ventricle. After proper position was established across the valve, the balloons were inflated simultaneously for 5 to 15 seconds, after which they were withdrawn into the descending aorta. In most patients only a single pair of inflations was performed, although in occasional patients dual balloon inflation was performed a second or third time. One balloon catheter with its accompanying guidewire was then removed, taking special care to apply negative pressure during the "delivery" of the balloon through the arteriotomy. The second exchange wire was left in place across the aortic valve while the remaining balloon catheter was exchanged for a diagnostic catheter and introducer sheath. Following completion of the postvalvuloplasty hemodynamic recordings and aortic root angiography, the catheter and sheath were removed. At the completion of the procedure, arteriotomy was extended proximally and distally to inspect for intimal trauma and then closed using a continuous suture of 5-0 prolene. The superficial fascia and skin were then closed in routine fashion.

Results

Clinical data including hemodynamic and angiographic findings in the 16 patients undergoing in vivo dual balloon valvuloplasty are summarized in Tables I and II and Figures 2 through 5.

Hemodynamic findings: Peak aortic valve gradient decreased from 79 ± 8 mm Hg (mean ± standard error of the mean) before valvuloplasty to 57 ± 7 after single balloon valvuloplasty ($p < 0.0005$) (Figure 2). Likewise, mean aortic valve gradient decreased from 56 ± 5 before to 42 ± 5 mm Hg ($p < 0.0005$) (Figure 3). Cardiac output did not change significantly (Figure 4). Calculated aortic valve area [10] increased from 0.45 ± 0.04 to 0.57 ± 0.05 cm^2 ($p < 0.0005$) (Figure 5).

Dual balloon valvuloplasty accomplished a further diminution in peak gradient from 57 ± 7 after single balloon valvuloplasty to 36 ± 4 mm Hg after double balloon valvuloplasty ($p < 0.0005$). Mean gradient decreased from 42 ± 5 to 27 ± 3 mm Hg ($p < 0.0005$). Cardiac output did not change significantly. Finally, calculated aortic valve area increased from 0.57 ± 0.05 after single balloon valvuloplasty to 0.77 ± 0.06 cm^2 after double balloon valvuloplasty ($p < 0.0005$).

The percent change in peak and mean gradients, cardiac output and aortic valve area are listed in Table II. The percent changes in peak and mean gradients and cardiac output after dual balloon valvuloplasty were *not* significantly different from the percent

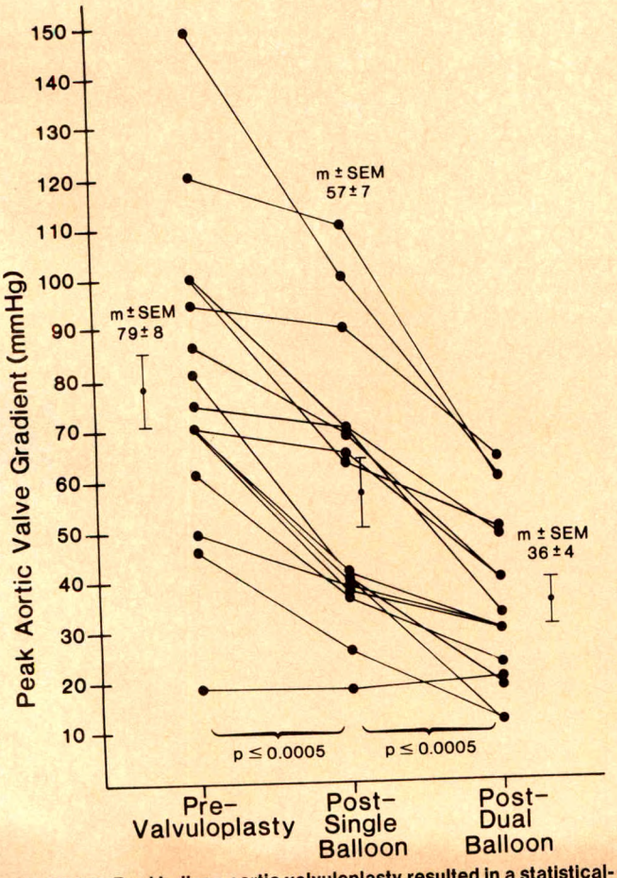

FIGURE 2. Dual balloon aortic valvuloplasty resulted in a statistically significant supplementary reduction in peak gradient beyond that achieved with a single balloon.

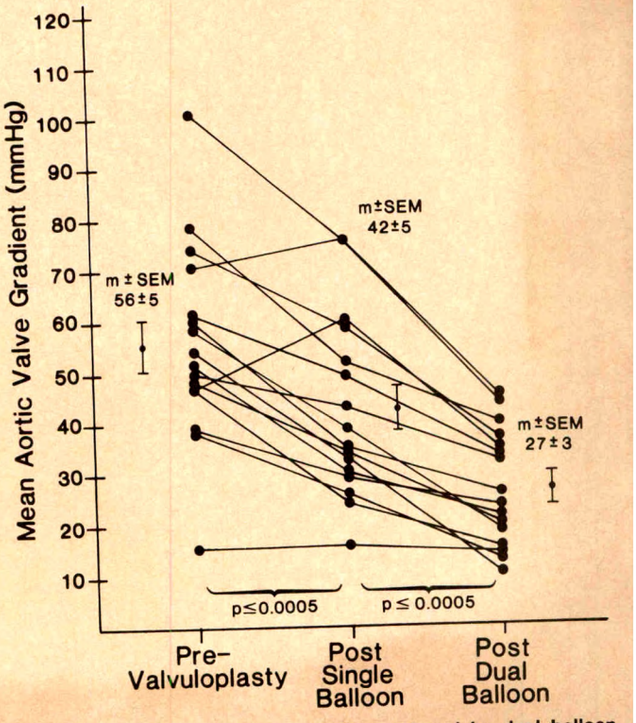

FIGURE 3. Mean gradient was further reduced by dual balloon inflation following completion of single balloon valvuloplasty.

TABLE I Patient, Catheterization and Hemodynamic Data in Dual Balloon Aortic Valvuloplasty

Pt	Age (yr), Sex	Catheters (Balloon diameter in mm)		Gradient (mm Hg)						Cardiac Output (liters/min)			AVA (cm^2)		
				Peak			Mean								
		SB	DB	Pre-	Post-SB	Post-DB	Pre-	Post-SB	Post-DB	Pre-	Post-SB	Post-DB	Pre-	Post-SB	Post-DB
1	74, F	20	18 + 20	148	100	60	101	76	44	3.9	3.8	3.8	0.3	0.4	0.6
2	84, F	20	15 + 20	120	110	60	71	76	45	1.5	2.8	2.8	0.2	0.3	0.5
3	76, F	20	20 + 15	100	63	50	78	52	39	3.5	4.1	4.4	0.4	0.5	0.7
4	65, M	15, 20, 25	15 + 15	100	70	48	74	58	36	6.3	5.2	7.0	0.5	0.7	1.1
5	67, F	20	18 + 18	95	90	64	47	59	35	2.2	2.1	2.1	0.3	0.3	0.4
6	69, M	20	18 + 18	86	68	40	62	49	33	4.9	4.6	4.8	0.7	0.7	1.0
7	67, M	20	20 + 18	82	40	18	59	38	18	5.1	*	4.3	0.6	*	1.0
8	72, F	15, 20	15 + 20	75	70	33	48	34	20	5.3	5.0	4.7	0.6	0.8	1.3
9	88, F	20	18 + 20	70	40	12	54	33	10	2.3	2.1	2.0	0.3	0.4	0.7
10	85, F	20	20 + 18	70	37	30	51	30	22	2.0	2.1	1.8	0.3	0.4	0.6
11	81, F	20	18 + 18	70	65	40	50	43	32	3.9	4.1	4.6	0.5	0.6	0.7
12	65, M	12, 15, 20	20 + 18	70	42	30	60	35	26	4.3	4.0	4.9	0.5	0.7	0.9
13	86, F	18	18 + 20	62	36	23	47	24	15	3.2	3.5	3.3	0.5	0.8	0.9
14	88, M	15, 20	15 + 18	50	38	30	39	28	24	3.7	3.8	4.2	0.5	0.7	0.8
15	88, M	20	18 + 18	46	26	12	38	26	13	2.9	3.2	3.3	0.4	0.6	0.8
16	79, M	20	15 + 18	18	18	20	16	16	14	3.4	2.6	2.6	0.7	0.7	0.5
			20 + 18												
Mean ± SEM				79 ± 8	57 ± 7	36 ± 4	56 ± 5	42 ± 5	27 ± 3	3.6 ± 0.3	3.5 ± 0.3	3.8 ± 0.4	0.45 ± 0.40	0.57 ± 0.05	0.77 ± 0.06
Paired *t* test				p ≤0.0005		p ≤0.0005	p ≤0.0005		p ≤0.0005	p = NS		p = NS	p ≤0.0005		p ≤0.0005

* Patient 7 had an atrial septal defect; because O_2 saturations were not obtained after single balloon dilation, cardiac output and aortic valve area could not be determined post-single balloon.
DB = double balloon; NS = difference not significant; SB = single balloon; SEM = standard error of the mean.

TABLE II Percent Change in Peak and Mean Gradients, Cardiac Output and Aortic Valve Area in 16 Patients Treated with Single, Followed by Dual Balloon Aortic Valvuloplasty

	Peak Gradient		Mean Gradient		Cardiac Output		AVA	
Pt	Decrease Post-SB (%)	Decrease Post-DB (%)	Decrease Post-SB (%)	Decrease Post-DB (%)	Change Post-SB (%)	Change Post-DB (%)	Increase Post-SB (%)	Increase Post-DB (%)
1	32	27	25	28	−3	0	33	66
2	8	45	−7	44	87	0	50	100
3	37	13	33	17	17	9	25	50
4	30	22	22	30	−17	29	40	8
5	5	27	−25	51	−5	0	0	33
6	21	33	21	26	−6	4	0	43
7	51	27	36	34	ND	ND	ND	ND
8	7	49	29	29	−6	−6	33	83
9	43	40	39	43	−9	−4	33	100
10	47	10	41	16	5	−15	33	66
11	7	36	14	22	5	13	20	20
12	40	17	42	15	−7	21	40	40
13	42	21	49	19	9	6	60	20
14	24	16	28	10	3	12	40	20
15	43	30	32	34	10	3	50	50
16	0	−11	0	13	−24	0	0	−29
Mean ± SEM	27 ± 4.3	25 ± 3.7	24 ± 4.9	27 ± 3.0	3.9 ± 6.5	4.8 ± 2.8	30 ± 48	49 ± 9.0
Paired *t* test	p = NS		p = NS		p = NS		p <0.025	

Percent change post-SB was determined according to following formula (PreV-Post SB)/PreV.
Percent change post-DB was determined according to following formula (Post-SB-Post DB)/PreV.
ND = not determined; other abbreviations as in Table I.

change observed after single balloon valvuloplasty. That is, the magnitude of supplementary hemodynamic improvement achieved using 2 balloons was equivalent to that achieved with 1 or a series of single balloons. As a result of the severely diminished prevalvuloplasty aortic valve area, however, the percent change in calculated aortic valve area after dual balloon valvuloplasty was significantly ($p < 0.02$) greater than the percent improvement in valve area observed after single balloon dilation.

Aortic regurgitation: Patients were examined for aortic regurgitation by auscultation, Doppler ultrasound or aortic root angiography before and after the valvuloplasty procedure, but not between single and dual balloon valvuloplasty. By auscultation, aortic regurgitation was either absent or unchanged in all 16 patients. On Doppler ultrasound examination, no patient had new or more aortic regurgitation. Of 8 patients in whom aortic root angiography was performed after valvuloplasty, only 1 had evidence of new or increased (0 to "trace") aortic regurgitation.

In 1 patient, the only patient in whom we have repeated balloon valvuloplasty because of restenosis after an initially successful procedure, laceration of the common femoral artery occurred during removal of the balloon catheters following completion of dual valvuloplasty. The same artery was used for first (single) and second (single and dual) valvuloplasty procedures. Inspection of the artery at the time of surgical repair disclosed a site of focal, fibrotic constriction near the laceration. This constriction presumably resulted from the previous cutdown/repair and may have predisposed to the laceration at the time of the repeat dilation. In a second patient with mitral stenosis as well as AS, cardiac tamponade developed approximately 1.5 hours after a hemodynamically successful procedure. The patient was taken to the operating room but failed to survive combined aortic and mitral valve replacement after repair of a perforated left ventricle.

Discussion

Despite the documented short-term efficacy of aortic balloon valvuloplasty, certain limitations remain. In the majority of patients reported to date, varying degrees of AS typically persist. Although it is clear that symptomatic improvement may occur in association with even a small increase in calculated orifice area, the extent to which the threat of sudden death is diminished when important valvular stenosis persists remains unknown.[11] Further, preliminary follow-up data have demonstrated that the hemodynamic results obtained immediately after valvuloplasty are by no means permanent, even during the first 6 months of follow-up. Whether the magnitude of hemodynamic improvement obtained at the time of the original valvuloplasty is the principal determinant of restenosis—as has been suggested in the case of pulmonary valvular stenosis[12]—also remains unknown. It is clear that modifications in catheter design and technique are required.

The data from the 16 patients described in the present study indicate that use of the dual balloon technique may improve the hemodynamic results that can be accomplished with 1 or a series of single balloons in selected adults with calcific AS. The dual balloon technique has been used by previous investigators to treat a variety of valvular and congenital lesions

Khan,[13] Radtke,[14] Rao[12] and their co-workers used the dual balloon technique for children in whom the angiographic diameter of the pulmonary valve anulus was ≥20 mm. Moore et at[15] used dual balloon valvuloplasty to treat an infant with recoarctation of the aorta. Al Zaibag et al[16] and others[17,18] have demonstrated that simultaneous inflation of 2 balloons accomplished a hemodynamic result that is generally superior to that observed with single balloon valvuloplasty.

The largest experience with the dual balloon technique was reported by Mullins et al[19] who used the technique to treat 41 patients, mostly children, with stenosis of the pulmonic, aortic, mitral and tricuspid valves and vena cava. Mullins selected patients for the dual balloon approach when the anular diameter of the stenotic lesion was large relative to available balloon diameter or when technical considerations obviated the use of larger balloon catheters. The 41 patients included 14 with AS; although the age and extent of valvular calcification was not clarified for this subgroup, the dual balloon technique reduced peak transvalvular gradient from an average of 68 before to 24 mm Hg after dual balloon inflation. Two patients had either new or slightly more aortic regurgitation postversus prevalvuloplasty, and 2 had transient left bundle branch block.

Finally, Dorros et al[20] recently reported application of a combined brachial-femoral dual balloon technique in 10 patients, using a peripheral vascular angioplasty balloon (maximum diameter 12 mm) in combination with up to 20 mm valvuloplasty balloons. Successful valvuloplasty was achieved in all 10 patients, and aortic valve area increased from 0.56 ± 0.3 to 1.03 ± 0.6 cm^2 ($p < 0.05$).

No serious complications were reported among these previously reported patients treated with dual balloon valvuloplasty. Our experience with the present group of 16 patients is similar in that no complications were observed that were directly attributable to the dual balloon technique.

In contrast to our patients, however, none of the previous investigations included serial hemodynamic evaluation of single followed by dual balloon valvuloplasty in the same individual patients. The findings reported here thus support both the acute efficacy, as well as the safety, of the dual balloon technique. Whether such improvement in acute hemodynamic outcome will translate into a superior long-term result remains to be determined.

The proper combination of balloon diameters for dual balloon valvuloplasty remains uncertain. Butto et al[21] found that in the case of dual balloon pulmonary valvuloplasty, both balloons retain their circular shape without effacement as long as the diameters of the 2 balloons are within 10 mm of each other and the combined diameters do not exceed the native pulmonary valve anular diameter by 90%. Further, it seems rea-

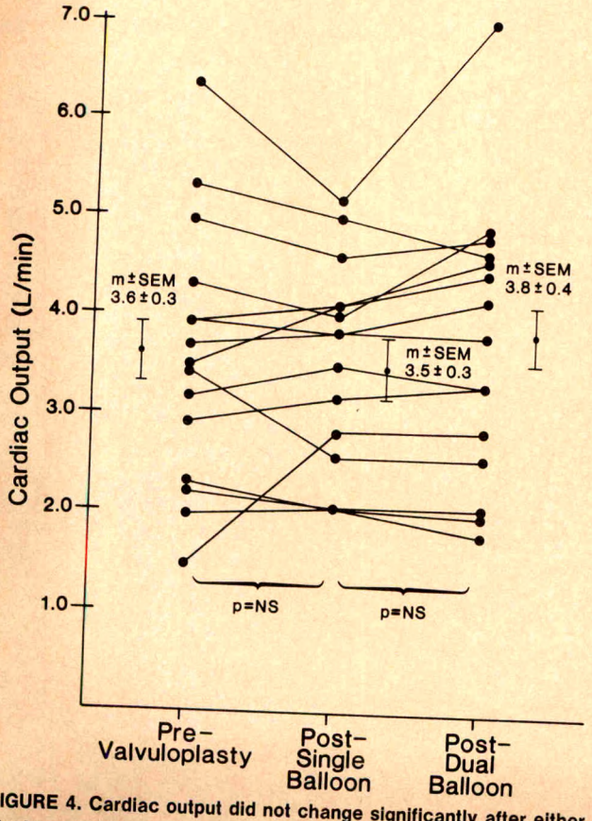

FIGURE 4. Cardiac output did not change significantly after either single or dual balloon valvuloplasty.

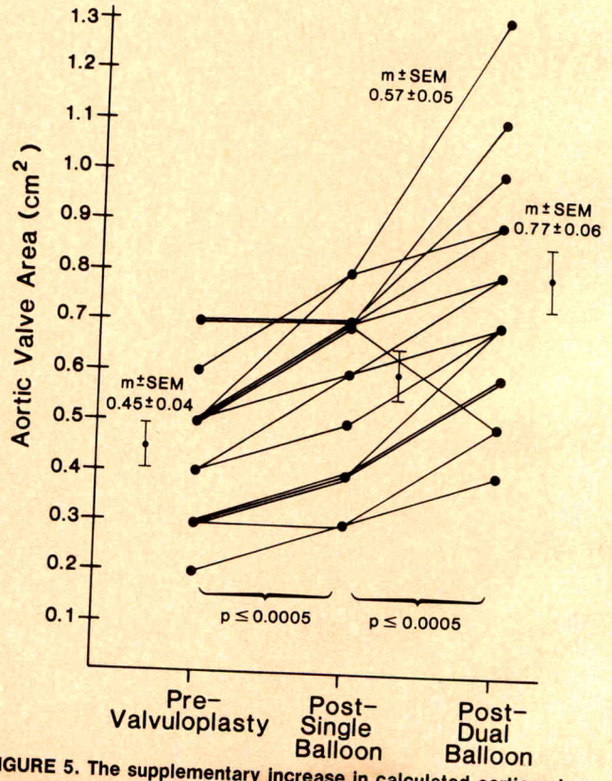

FIGURE 5. The supplementary increase in calculated aortic valve area accomplished with dual balloon dilation was highly statistically significant compared to that achieved with single balloon inflation.

sonable to use a combined diameter that exceeds that of the largest single balloon employed. How much in excess of 20 mm diameter (or 314 mm^2 in corresponding cross-sectional area) the combined balloon diameter/area should be must represent a compromise between efficacy and safety. Mullins et al[19] have recommended that for dual balloon aortic valvuloplasty, the sum of the inflated diameters should equal 1.2 or 1.3 times the aortic valve anular diameter. Although we observed no serious complications, Ring et al[22] have previously shown that if balloon diameter in the case of single balloon pulmonary valvuloplasty exceeds 30% of the native pulmonary valve diameter, hemorrhage into the right ventricular myocardium may occur. We are likewise aware of at least 1 published report[23] and 1 unpublished (personal communication, Mansfield Scientific) of anular rupture associated with single balloon valvuloplasty. Thus, the upper safe limit of balloon diameter/area—whether single or double—remains to be determined.

Addendum: Since the initial submission of this manuscript, we have used the dual balloon technique in 5 additional patients with similar results. The most recent application was performed using an exclusively percutaneous approach, made possible by the availability of lower profile balloon catheters (up to 20 mm diameter [Mansfield Scientific]) that can be introduced and removed via a 12Fr sheath. In the case of this 91-year-old woman, 18 and 20 mm balloons were passed simultaneously without complications via the right and left femoral arteries, increasing aortic valve area from 0.49 to 0.82 cm^2.

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Effect of Mitral Regurgitation on Diastolic Filling with Left Ventricular Hypertrophy

M. ABUBAKR SHAIKH, MD, and STEVEN J. LAVINE, MD

Earlier studies have suggested that mitral regurgitation (MR) augments early left ventricular (LV) diastolic filling. To determine whether MR affects early diastolic filling in patients with abnormal diastolic filling, transmitral pulsed-wave Doppler recordings were used to study 32 normal subjects, 21 patients with LV hypertrophy, 23 with LV hypertrophy and MR and 15 patients with MR. Patients with MR had increased peak early filling velocities (MR 108 ± 27 cm/s, normal 80 ± 16 cm/s, $p < 0.01$), peak atrial filling velocities (MR 72 ± 18 cm/s, normal 55 ± 12 cm/s, $p < 0.05$) and increased deceleration rates (MR 5.0 ± 1.9 m/s^2, normal 3.5 ± 1.2 m/s^2, $p < 0.05$). Patients with LV hypertrophy had reduced peak early filling velocities (69 ± 14 cm/s, $p < 0.05$) and increased peak atrial filling velocities (83 ± 16 cm/s, $p < 0.001$). There was also an increase in the atrial filling fraction and reduction in the rapid filling fraction as compared with normal patients. Patients with LV hypertrophy and MR had increased peak early filling velocities (98 ± 26 cm/s, $p < 0.01$ vs normal, $p < 0.001$ vs LV hypertrophy patients), increased atrial filling velocities (84 ± 27 cm/s, $p < 0.001$ vs normal), increased deceleration rates (4.4 ± 2.4 m/s^2, $p < 0.05$ vs normal) and a normal distribution of diastolic filling. Within the LV hypertrophy and MR group, diastolic filling parameters were similar when patients were subgrouped on the basis of auscultability of MR. MR augments early diastolic filling and may tend to normalize diastolic filling patterns in LV hypertrophy patients. The use of diastolic filling to evaluate diastolic function in patients with MR should be used with caution.

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Enhanced early left ventricular (LV) diastolic filling has been reported in patients with mitral regurgitation (MR).[1,2] Presumably, enhanced early diastolic filling is the result of an increased left atrial-LV pressure gradient early in diastole, produced by the V wave of MR.[1,3,4] We hypothesized that MR may alter the LV diastolic filling pattern by enhancing early diastolic filling in patients with heart disease known to produce abnormal diastolic filling. Concentric LV hypertrophy due to a variety of causes is one such entity known to be associated with abnormal diastolic filling.[5–7] In the present study, we evaluated the diastolic filling patterns in patients with concentric LV hypertrophy, combined LV hypertrophy and MR, patients with MR and patients without heart disease using pulsed-wave Doppler recordings of transmitral flow velocity. Measurements of transmitral flow velocity had been found to be useful in characterizing diastolic filling.[8,9]

From the Section of Cardiology, Department of Internal Medicine, Harper Hospital, Wayne State University, Detroit, Michigan. Manuscript received May 18, 1987; revised manuscript received and accepted November 2, 1987.

Address for reprints: Steven J. Lavine, MD, Noninvasive Laboratory, Harper Hospital, 3990 John R. Street, Detroit, Michigan 48201.

Methods

Patients: We reviewed the M-mode, 2-dimensional and Doppler recordings of all patients referred to the Noninvasive Laboratory by their primary care physicians between August 1985 and March 1986. From this review, the recordings of 91 patients with sinus rhythm received a detailed evaluation of diastolic function if they were assignable to 1 of 4 groups. Group 1 consisted of 32 patients who had a normal history, physical examination, electrocardiogram and echocardiogram (M-mode, 2-dimensional and Doppler). Patients with a history of hypertension, use of calcium antagonists or who had LV hypertrophy were excluded. The presence of LV hypertrophy was assessed by M-mode evidence of septal or posterior wall thickness ≥12 mm. Group 2 consisted of 21 patients referred for evaluation of LV systolic function who had evidence of LV hypertrophy, M-mode fractional shortening ≥30% and no heart disease revealed by history, physical ex-

amination, electrocardiogram or echocardiogram. All patients in group 2 had hypertension and were being treated. β blockers were being used by 7. Patients using calcium antagonists were excluded. Group 3 comprised 23 patients also referred for evaluation of LV systolic function, who fulfilled the criteria for group 2 but in addition presented evidence of MR detected by pulsed-wave Doppler. Hypertension was present and treated in 20 patients, aortic stenosis was found in 3 and β-blockers were being used by 8. The cause of MR was ascribed to mitral anular calcification in 8, mitral valve prolapse in 5, calcified papillary muscle in 1 and was undetermined in 10. MR was considered to be mild in 11 patients, moderate in 11 and severe in 1. MR was auscultable in 9 and nonauscultable in 14. Patients using calcium antagonists were excluded. Group 4 consisted of 15 patients with a history of chronic MR and evidence of MR by pulsed-wave Doppler who did not have LV hypertrophy or other evidence of heart disease as assessed by history, physical examination, electrocardiogram or echocardiogram. Patients with a history of hypertension or use of calcium antagonists were excluded from this group. MR was ascribable to anular calcification in 6, mitral valve prolapse in 4 and was undetermined in 5. MR was considered to be mild in 8 patients, moderate in 6 and severe in 1.

M-mode and two-dimensional echocardiograms: All 91 patients had M-mode and 2-dimensional studies performed with a 3.5 MHz transducer (IREX Meridian, Johnson and Johnson). Patients with regional wall-motion abnormalities were excluded from the study. From the parasternal short-axis-derived M-modes of the LV, the interventricular septal thickness, posterior wall thickness, end-diastolic and end-systolic dimensions were obtained according to the recommendations of the American Society of Echocardiography.[10] Fractional shortening was calculated in the standard manner.[10] LV mass index was obtained using the M-mode cube function method of Devereaux and Reichek.[11]

Doppler studies: Pulsed- and continuous-wave Doppler studies were performed with a combined 2-dimensional phased array scanner (IREX Meridian) and a continuous and range-gated pulsed-wave Doppler (2.0 and 3.0 MHz). Full velocity signals were recorded on a strip-chart recorder or on video tape with an effective paper speed of 75 mm/s. Patients were examined in the left lateral position with the transducer placed at the apex to visualize the apical 4-chamber or long-axis view. Sample volume locations within the left atrium were varied in order to make a careful search for holosystolic turbulent flow suggesting MR. The diagnosis of MR was made when holosystolic turbulent flow was found in the left atrium. The severity of MR was determined by mapping of the left atrium. Holosystolic flow disturbances found at the level of the valve or 1 cm above were considered to be mild. Flow disturbances between 1 cm above the mitral valve to the midportion of the left atrium were considered to be moderate. Flow disturbances found extending from the midportion of the left atrium to the left atrial posterior wall or into the pulmonary veins were considered to be severe. Transmitral flow recordings were obtained by placing the sample volume in the mitral orifice, close to the tips of the mitral leaflets in diastole. Flow velocity recordings were not corrected for the angle between the Doppler flow direction and assumed mitral flow direction because the angle was always <20° (<6% error).

Transmitral flow measurements: Figure 1 is a graphic illustration of a normal flow velocity recording of transmitral flow. For each transmitral flow measurement, 5 consecutive spectral tracings were evaluated and averaged using a hand-controlled joystick and a computer-based analysis package (IREX Meridian Measurement and Analysis, Johnson and Johnson). We obtained the peak rapid filling velocity and peak atrial filling velocity in cm/s. The peak rapid filling velocity divided by the peak atrial filling velocity was also obtained as an additional transmitral flow velocity measurement. The rapid filling period was defined as the time interval from the onset of mitral flow to the end of rapid filling. The end of rapid filling was determined as a discernible point in time following the peak rapid filling velocity when the flow velocity curve plateaus (diastasis) or at the point when the flow velocity begins to rise. Similarly, the atrial filling period was defined as the onset of atrial filling to the end of mitral flow. The onset of atrial filling was determined as the point when a rise in flow velocity following a plateau (diastasis) or as the point when the flow velocity tracing accelerates following the end of the rapid filling period. The diastolic filling period was defined as the time interval from the onset to the end of transmitral flow. In this study, a wall filter of 0.12 m/s was used. Because the wall filter in this instrument produced a "velocity cutoff" at 0.12 m/s, we extrapolated the spectral tracings perpendicularly to the

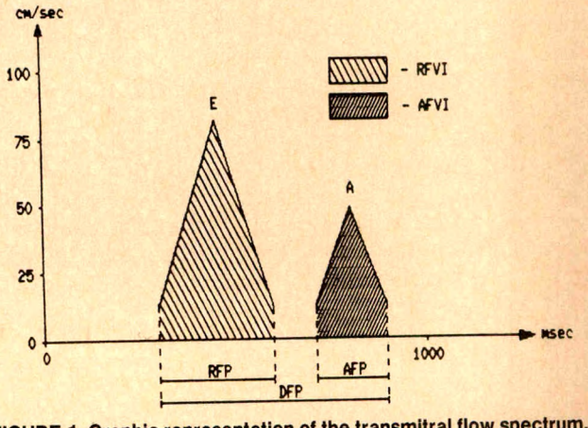

FIGURE 1. Graphic representation of the transmitral flow spectrum, which can be divided into a rapid filling period (RFP) and an atrial filling period (AFP). The area under the rapid filling spectrum (RFVI) or the atrial filling spectrum (AFVI) represents the amount of diastolic filling occurring during the rapid filling or atrial filling period. The peak rapid filling velocity (E) and the peak atrial filling velocity (A) are shown. DFP = diastolic filling period.

TABLE I Age and Echocardiographic Variables

	Normal Patients (n = 32)	Patients with MR (n = 15)
Age (yr)	46 ± 14	48 ± 14
End-diastolic dimension (mm)	49 ± 5	52 ± 6
Fractional shortening (%)	40 ± 6	38 ± 7
Septal thickness (mm)	9 ± 1	9 ± 1
Posterior wall thickness (mm)	9 ± 1	9 ± 1
LV mass (g/m^2)	83 ± 14	89 ± 20

LV = left ventricular; MR = mitral regurgitation.

TABLE II Parameters of Diastolic Filling

	Normal Patients (n = 32)	Patients with MR (n = 15)
Peak rapid filling velocity (cm/s)	80 ± 16	108 ± 27*
Peak atrial velocity (cm/s)	55 ± 12	72 ± 18†
E/A	1.5 ± 0.4	1.5 ± 0.3
Deceleration rate (m/s^2)	3.5 ± 1.2	5.0 ± 1.9†
RR (ms)	879 ± 156	843 ± 88
Diastolic filling period (ms)	490 ± 160	474 ± 102
Rapid filling period (ms)	238 ± 74	271 ± 70
Rapid filling fraction (%)	0.64 ± 0.11	0.65 ± 0.04
Atrial filling period (ms)	149 ± 37	170 ± 26
Atrial filling fraction (%)	0.31 ± 0.09	0.31 ± 0.06

* $p < 0.01$; † $p < 0.05$.
E/A = peak rapid filling velocity/peak atrial velocity; LV = left ventricular; MR = mitral regurgitation; RR = cycle length.

TABLE III Age and Echocardiographic Variables

	Normal Patients (n = 32)	Patients with LVH (n = 21)	Patients with LVH & MR (n = 23)
Age (yr)	46 ± 14	51 ± 15	54 ± 13
End diastolic dimension (mm)	49 ± 5	44 ± 5*	46 ± 7
Fractional shortening (%)	40 ± 6	44 ± 8	44 ± 9
Septal thickness (mm)	9 ± 1	15 ± 3†	15 ± 3†
Posterior wall thickness (mm)	9 ± 1	14 ± 3†	15 ± 3†
LV mass (g/m^2)	83 ± 14	141 ± 40†	149 ± 35†

* $p < 0.05$, † $p < 0.001$ versus normal subjects.
LVH = left ventricular hypertrophy patients; MR = mitral regurgitation patients.

TABLE IV Parameters of Diastolic Filling

	Normal Patients (n = 32)	Patients with LVH (n = 21)	Patients with LVH & MR (n = 23)
Peak rapid filling velocity (cm/s)	80 ± 16	69 ± 14*	98 ± 26†¶
Peak atrial velocity (cm/s)	55 ± 12	83 ± 16‡	84 ± 27‡
E/A	1.5 ± 0.4	0.9 ± 0.2‡	1.3 ± 0.4*‖
Deceleration rate (M/s^2)	3.4 ± 1.2	3.1 ± 1.7	4.4 ± 2.4*§
RR (ms)	879 ± 156	821 ± 151	884 ± 140
Diastolic filling period (ms)	490 ± 160	462 ± 125	499 ± 126
Rapid filling period (ms)	238 ± 74	244 ± 49	280 ± 97
Rapid filling fraction (%)	0.64 ± 0.11	0.55 ± 0.10†	0.65 ± 0.12‖
Atrial filling period (ms)	149 ± 37	182 ± 56	176 ± 57
Atrial filling fraction (%)	0.31 ± 0.09	0.45 ± 0.09‡	0.35 ± 0.10‖

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$ versus normal subjects; § $p < 0.05$, ‖ $p < 0.01$, ¶ $p < 0.001$ for LVH versus LVH & MR.
Abbreviations as in Tables II and III.

baseline. All timing measurements were taken from the baseline. The area beneath the spectral tracing was determined for the rapid filling, atrial filling and diastolic filling periods. Both rapid filling and atrial filling areas were divided by the diastolic filling area to generate a rapid filling and atrial filling fraction.

The deceleration rate following the peak rapid filling velocity was determined for each of the 4 groups. Briefly, the spectral tracing after the peak rapid filling velocity and before the atrial filling was examined and the deceleration slope obtained.

Statistical methods: Comparison among the 4 groups of patients for different echocardiographic and Doppler parameters were carried out by a 1-way analysis of variance. If statistical significance was obtained ($p < 0.05$), multiple comparison *t* tests were used to find out where significant differences existed. A p value of < 0.05 was considered significant. Data were expressed as mean ± standard deviation.

Results

The results of age, wall thickness, LV size, mass and function for normal subjects and patients with MR are listed in Table I. No significant differences were found between groups. Table II presents the parameters of diastolic filling for normal patients and those with MR. Both peak rapid filling velocity and peak atrial velocity were increased in the group with MR. There were no significant differences in any filling interval or in the rapid or atrial filling fraction. The deceleration rate was increased in the group with MR. Figure 2 shows a spectral tracing of transmitral flow for a normal subject (left) and a patient with MR (right). Both the early peak filling velocity and atrial filling velocity were increased as compared with the normal patient.

Table III summarizes the results of age, wall thickness, LV dimension, mass and function for normal subjects, patients with LV hypertrophy and patients with both LV hypertrophy and MR. The end-diastolic dimension was smaller in the group with LV hypertrophy as compared with the normal subjects. According to the entry criteria for this study, the posterior and septal wall thicknesses were increased in the groups with LV hypertrophy and LV hypertrophy with MR. In comparison with the normal subjects, LV mass was increased in the groups with LV hypertrophy and LV hypertrophy and MR. The diastolic filling parameters for normal subjects, patients with LV hypertrophy and those with LV hypertrophy and MR are listed in Table IV. The group with LV hypertrophy demonstrated a reduced peak rapid filling velocity, increased atrial filling velocity and reduced early peak rapid filling velocity/atrial filling velocity ratio as compared with the normal group. The rapid filling fraction was reduced while the atrial filling fraction was increased, in comparison with normal subjects. The group with LV

hypertrophy and MR demonstrated higher peak early filling velocities as compared with normal patients and the group with LV hypertrophy. The peak atrial filling velocity also was increased as compared with normal subjects and was similar to the group with LV hypertrophy. The peak early filling velocity/atrial filling velocity ratio was intermediate between normal subjects and patients with LV hypertrophy and significantly different from both. The rapid filling and atrial filling fractions were similar to those of normal subjects but significantly greater for the rapid filling fraction and significantly less for the atrial filling fraction as compared with the patients with LV hypertrophy. The deceleration rate was significantly greater in the group with LV hypertrophy and MR as compared with normal patients and those with LV hypertrophy. Figure 3 shows spectral tracings of transmitral flow for a patient with LV hypertrophy (left) and a patient with LV hypertrophy and MR (right). There was reduced early peak filling velocity and increased atrial filling velocity in the patient with LV hypertrophy as compared with the normal subject (Figure 2). In the patient with LV hypertrophy and MR, the early filling and atrial filling velocities were increased as compared with the normal group. The early filling velocity and atrial filling velocity peaks were nearly similar in height, that is, qualitatively different from the patient with LV hypertrophy.

Regarding the patients with MR and LV hypertrophy, 9 had auscultable MR and 14 nonauscultable MR. In the auscultable group, MR was mild in 4, moderate in 4 and severe in 1. In the nonauscultable group, 7 had mild and 7 had moderate MR. Table V lists the diastolic filling parameters for these 2 subgroups of patients and reveals no significant differences between them.

Discussion

In the present study, we sought to address the issue of whether MR could produce apparent normalization of early diastolic filling in patients with LV hypertrophy, an entity known to be associated with a high incidence of abnormal diastolic filling. In our patient selection process, we evaluated consecutive patient records meeting our criteria for patient inclusion. The use of β blockers in the patients with LV hypertrophy and LV hypertrophy with MR may have affected diastolic filling parameter determinations in those with blood pressure responses to therapy.[12] However, one-third of patients with LV hypertrophy and LV hypertrophy with MR were using β blockers as effective therapy for hypertension. Both groups had comparable degrees of MR and a similar distribution of etiologies (MR was mild in approximately 50%, which may explain why the end-diastolic dimension was not significantly increased as compared with normal subjects). Although no attempt at age matching was made, the mean group ages were comparable, minimizing age as a factor affecting diastolic filling.[13]

The data in this study indicate that peak early filling velocities, deceleration rate and atrial filling velocities were increased in patients with MR. Furthermore, diastolic filling was normally distributed between the rapid filling period and atrial filling period. Patients with LV hypertrophy had reduced peak early filling velocity, increased atrial velocity and a greater extent of filling during the atrial filling period. These findings in patients with LV hypertrophy were similar to those of previous studies.[5,14] Patients with LV hypertrophy and MR demonstrated increased peak early velocities, increased deceleration rate and elevated peak atrial velocities. The ratio of peak early to peak atrial velocity was intermediate between the normal subjects and the patients with LV hypertrophy. The distribution of

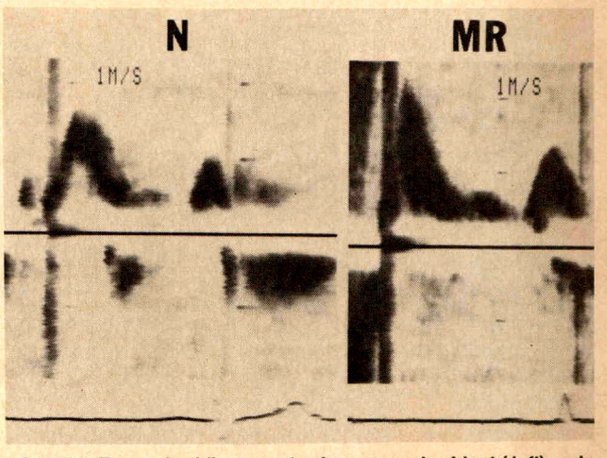

FIGURE 2. Transmitral flow spectra for a normal subject (*left*) and a patient with mitral regurgitation (*right*). There is an increase in both the peak rapid filling and peak atrial filling velocity. N = normal; MR = mitral regurgitation.

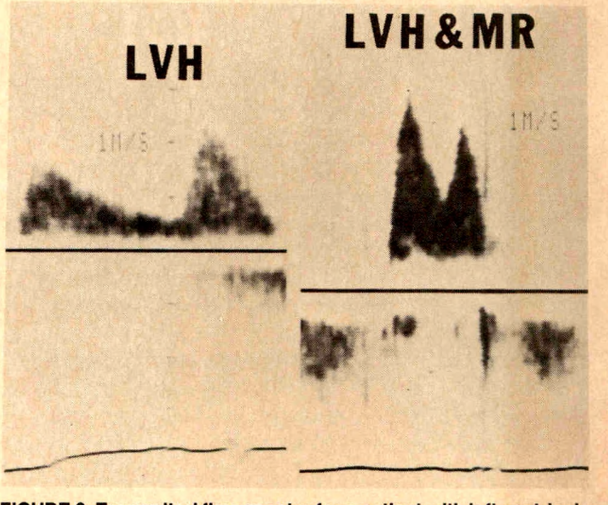

FIGURE 3. Transmitral flow spectra for a patient with left ventricular hypertrophy (*left*) and another with left ventricular hypertrophy and mitral regurgitation (*right*). The patient with left ventricular hypertrophy (LVH) demonstrates a reduced peak rapid filling velocity, increased atrial filling velocity and a ratio of peak rapid filling velocity/peak atrial filling velocity <1. The patient with left ventricular hypertrophy and mitral regurgitation (LVH&MR) had both increased peak rapid filling and peak atrial filling velocities as compared with normal subjects with a peak rapid filling velocity/peak atrial filling velocity >1.

TABLE V Diastolic Filling Parameters and Auscultability of Mitral Regurgitation

	Auscultable LVH & MR (n = 9)	Nonauscultable LVH & MR (n = 14)
Peak rapid filling velocity (cm/s)	104 ± 23	95 ± 22
Peak atrial velocity (cm/s)	86 ± 26	82 ± 29
E/A	1.3 ± 0.4	1.2 ± 0.4
Rapid filling fraction (%)	0.64 ± 0.16	0.66 ± 0.13
Atrial filling fraction (%)	0.36 ± 0.10	0.34 ± 0.12

Abbreviations as in Tables II and III.

diastolic filling was similar to that of normal subjects. The group with LV hypertrophy and MR was comparable in every way to the patients with LV hypertrophy, save for the presence of mitral regurgitation. Auscultability was not associated with a greater severity of MR, nor did it affect the diastolic filling characteristics as compared with those patients in which MR was not audible.

The data from patients with MR was comparable with M-mode echocardiographic and ventriculographic data previously reported in 2 studies,[1,2] both having reported an increase in the peak rapid filling rate. The peak atrial filling rate was not evaluated in these studies, but the atrial contribution of diastolic filling was similar to that of normal subjects. Although no study has yet evaluated the combined MR and LV hypertrophy, 1 study in hypertrophic cardiomyopathy patients demonstrated increased early rapid filling velocity in the obstructive type characterized by a high proportion of patients with MR.[15] Furthermore, the presence of MR in patients with dilated cardiomyopathy has been suggested as a reason for normalized early rapid filling velocities[16] and peak rates of filling noted among them.[17]

The present study retrospectively assessed diastolic filling characteristics in patients who had LV hypertrophy with or without MR. The mechanisms for these findings, at best, can only be speculated without simultaneous left atrial and left ventricular pressure recordings. Because the rate and extent of early diastolic filling has been demonstrated to be dependent on the magnitude and time course of the transmitral gradient,[18] we can hypothesize that the increased rate of early diastolic filling was probably due to an increased transmitral gradient contributed by the V wave of MR. The rapid decline in left atrial pressure (and the left atrial-left ventricular pressure gradient) following the V wave may be responsible for the increased rates of deceleration noted in both patients with MR and LV hypertrophy with MR: an attractive explanation for both types of patient. As to why late filling velocities were enhanced in MR patients is unclear, but may reflect an increase in total filling volume. In patients with MR and LV hypertrophy, late diastolic filling velocities were increased and similar to velocities in patients with LV hypertrophy. This may relate more to the underlying hypertrophy, which has a tendency to produce increased late filling velocities.[5-7] The normalization of the rapid filling fraction may be secondary to most of the regurgitant volume returning to the LV in early diastole. The failure to further increase late diastolic velocities is unclear. However, without simultaneous left atrial, left ventricular pressures and left ventricular volume to assess transmitral gradient and compliance, these explanations are speculative.

Clinical implications: The use of diastolic filling parameters and in particular the E/A ratio can be quite misleading if MR is present, especially in patients with LV hypertrophy or coronary disease. Caution should be exercised in interpreting diastolic filling parameters as estimates of diastolic function in the presence of MR. As both gated blood pool scintigraphy and M-mode can be used to assess diastolic filling and both do not directly assess the presence of MR, diastolic filling analysis by these techniques can be misleading. Furthermore, the use of physical examination to exclude MR may not be accurate, considering that 14 of 23 patients had nonauscultable MR in this study. Transmitral Doppler assessment of blood velocity may be preferable to other methods to evaluate diastolic filling in that it may alert us to the presence of MR.

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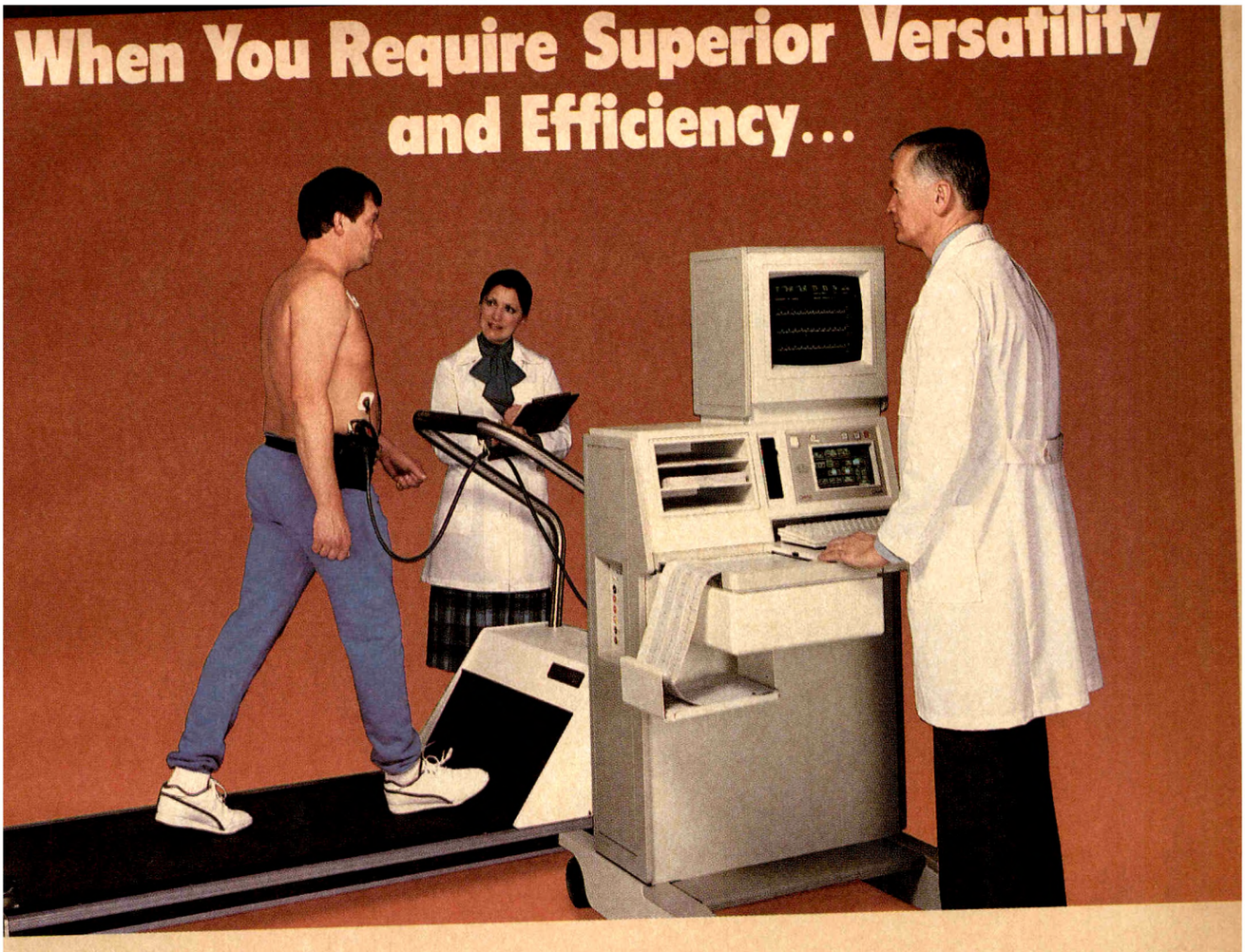

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Tambocor is indicated for the treatment of documented life-threatening ventricular arrhythmias, such as sustained V-tach.

Tambocor is also indicated for the treatment of patients with symptomatic NSVT and frequent PVCs. Because of the proarrhythmic effects of Tambocor, its uses in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of antiarrhythmic treatment outweigh the risks.

For most patients, the better choice.

Joan Borra's symptomatic PVCs and NSVT have been successfully controlled by Tambocor® (flecainide acetate) B.I.D. for almost a year, and she experienced none of the problems characteristic of arrhythmia therapy. Tambocor has proven to be highly effective in study after study. In a multicenter clinical trial against quinidine, for example, Tambocor produced greater than 95% suppression of NSVT in 86% of patients.[1] In a 12-month follow-up to this trial, 94% of patients who remained on Tambocor had 100% suppression of NSVT.[2]

Tambocor is so well tolerated by most patients that discontinuation due to noncardiac adverse effects in a major multicenter study was only 5.4%.[3] Tambocor also has convenient b.i.d. dosing, making it easier to comply with in long-term use.

Tambocor has a low incidence of cardiac side effects in patients with symptomatic PVCs and NSVT. In a study of 1,330 patients treated with Tambocor, the overall incidence of proarrhythmia was 6.8%. In patients with PVCs, the incidence was 1.7% (8/470); in NSVT patients, 3.8% (18/469).[4] However, Tambocor should be used with caution and dosed differently in patients with sustained V-tach, particularly those with congestive heart failure or myocardial dysfunction. The incidence of cardiac adverse effects has been found to be substantially higher in these patients. Please see full prescribing information.

This exceptional record of efficacy, safety and tolerance has been borne out in six years' experience with more than 300,000 patients worldwide. It's no wonder that many physicians prefer Tambocor for the treatment of symptomatic PVCs and NSVT.

Please see following page for brief summary of full prescribing information.

TAMBOCOR® B.I.D.
(flecainide acetate)

The one to start with, the one to stay with.

TAMBOCOR® B.I.D.
(flecainide acetate)

Brief Summary. Consult the package insert for full prescribing information.

CONTRAINDICATIONS:
TAMBOCOR is contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:
Proarrhythmic Effects. TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of TAMBOCOR, three fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias. In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Proarrhythmic effects were reported in 7% of patients treated with TAMBOCOR. Their frequency appears to be related to dose and to the underlying cardiac disease.
Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%; moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 0.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule (see Dosage and Administration).
Patients with less serious arrhythmias (chronic PVCs and nonsustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal.
The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease (see Dosage and Administration).
Heart Failure. TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. Exacerbation of preexisting CHF occurred more commonly in studies which included patients with class III or IV failure than in studies which excluded such patients. TAMBOCOR should be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dosage in such patients should be no more than 100 mg bid (see Dosage and Administration) and patients should be monitored carefully. Close attention must be given to maintenance of cardiac function, including optimization of digitalis, diuretic, or other therapy. In cases where CHF has developed or worsened during treatment with TAMBOCOR, the time of onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretics, others may require dosage reduction or discontinuation of TAMBOCOR. When feasible, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 μg/ml.
Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose-related increases in PR, QRS, and QT intervals.
PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one third of patients may develop new first degree AV heart block (PR interval ≥0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In one study, 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus, caution should be used when such intervals occur, and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes-type arrhythmia associated with TAMBOCOR induced QT prolongation and bradycardia.
Clinically significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second-degree AV block (0.5%) and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects (see Dosage and Administration). If second- or third-degree AV block, or right bundle branch block associated with a left hemiblock occurs, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.
Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.
Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.
The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally threshold changes are within the range of multiprogrammable pacemakers and, when these occur, a doubling of either voltage or pulse width is usually sufficient to regain capture.
Electrolyte Disturbances. Hypokalemia or hyperkalemia may alter the effects of class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR.

PRECAUTIONS:
Drug Interactions. TAMBOCOR has been administered to patients receiving digitalis preparations or beta-adrenergic blocking agents without adverse effects. During administration of multiple oral doses of TAMBOCOR to healthy subjects stabilized on a maintenance dose of digoxin, a 13% ± 19% increase in plasma digoxin levels occurred at six hours postdose.
In a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently, plasma flecainide levels were increased about 20% and propranolol levels were increased about 30% compared to control values. In this formal interaction study, TAMBOCOR and propranolol were each found to have negative inotropic effects; when the drugs were administered together, the effects were additive. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive. In TAMBOCOR clinical trials, patients who were receiving beta blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.
Flecainide is not extensively bound to plasma proteins. In vitro studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (e.g., anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction. Limited data in patients receiving known enzyme inducers (phenytoin, phenobarbital, carbamazepine) indicate only a 30% increase in the rate of flecainide elimination. In healthy subjects receiving cimetidine (1 gm daily) for one week, plasma flecainide levels increased by about 30% and half-life increased by about 10%.
When amiodarone is added to flecainide therapy, plasma flecainide levels may increase two-fold or more in some patients, if flecainide dosage is not reduced. (See Dosage and Administration.)
There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgement of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with nifedipine or diltiazem to recommend concomitant use.
Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg/kg/day (assuming patient weight of 50 kg) have not revealed any compound-related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.
Pregnancy. Pregnancy Category C. Flecainide has been shown to have teratogenic effects (club paws, sternebrae and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times (but not three times) the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg/day, respectively; however, delayed sternebral and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery, or increases the possibility of forceps delivery or other obstetrical intervention.
Nursing Mothers. Limited data suggest that flecainide is excreted in human milk. Because of the drug's potential for serious adverse effects in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.
Hepatic Impairment. Since flecainide elimination from plasma can be markedly slower in patients with significant hepatic impairment, TAMBOCOR should not be used in such patients unless the potential benefits clearly outweigh the risks. If used, frequent and early plasma level monitoring is required to guide dosage (See Plasma Level Monitoring); dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days).

ADVERSE EFFECTS:
The most serious adverse effects reported for TAMBOCOR, described in detail in Warnings section, were new or exacerbated ventricular arrhythmias which occurred in 7% of patients, and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest, about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/ml.
There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established. In foreign postmarketing surveillance studies, there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure, and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.
Incidence figures for other adverse effects are based on a multicenter efficacy study, utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to non-cardiac adverse effects.

Table 1
Most Common Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study

	Incidence in All	Incidence by Dose During Upward Titration		
Adverse Effect	429 Patients at Any Dose	200 mg/ Day (N=426)	300 mg/ Day (N=293)	400 mg/ Day (N=100)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance†	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.
†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400-600 mg/day, the incidence of these adverse experiences was similar, except for dizziness (32%) and visual disturbances (28%).
The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies: *Body as a Whole*—malaise, fever; *Cardiovascular*—tachycardia, sinus pause or arrest; *Gastrointestinal*—vomiting, diarrhea, dyspepsia, anorexia; *Skin*—rash; *Visual*—diplopia; *Nervous System*—hypoesthesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus; *Psychiatric*—anxiety, insomnia, depression.
The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients: *Body as a Whole*—Swollen lips, tongue and mouth; arthralgia, bronchospasm, myalgia; *Cardiovascular*—angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension; *Gastrointestinal*—flatulence; *Urinary System*—polyuria, urinary retention; *Hematologic*—leukopenia, thrombocytopenia; *Skin*—urticaria, exfoliative dermatitis, pruritus; *Visual*—eye pain or irritation, photophobia, nystagmus; *Nervous System*—twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor; *Psychiatric*— amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

HOW SUPPLIED:
TAMBOCOR is supplied as white, round, scored tablets containing 100 mg of flecainide acetate and embossed with RIKER on one side and TR 100 on the other side.

Manufactured by:
Riker Laboratories, Inc./3M
St. Paul, Minnesota 55144

TR-5A

References: 1. The Flecainide-Quinidine Research Group: Flecainide versus quinidine for treatment of chronic ventricular arrhythmias: A multicenter clinical trial. *Circulation* 1983;67:1117. **2.** Hodges M, Salerno DM, Granrud G, et al: Flecainide versus quinidine: Results of a multicenter trial. *Am J Cardiol* 1984;53(5):66B. **3.** Tambocor® (flecainide acetate) prescribing information, Riker Laboratories, Inc. **4.** Morganroth J, Anderson JL, Gentzkow GD: Classification by type of ventricular arrhythmia predicts frequency of adverse cardiac events from flecainide. *J Am Coll Cardiol* 1986;8:607.

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Noninvasive Assessment of Hemodynamic Responses to Exercise in Pulmonary Regurgitation After Operations to Correct Pulmonary Outflow Obstruction

GERALD R. MARX, MD, RICHARD W. HICKS, PhD, HUGH D. ALLEN, MD, and STANLEY J. GOLDBERG, MD

The influence of pulmonary regurgitation (PR) on exercise capacity is unknown. The hemodynamic responses to exercise in postoperative patients with PR was determined using Doppler-measured regurgitant fraction to indicate PR severity. Maximal heart rate, oxygen consumption and workload capacity were measured during upright cycle ergometry. Cardiac output was measured at rest and during submaximal supine cycle ergometry by pulsed Doppler echocardiography. Oxygen consumption was simultaneously measured and exercise factor was calculated as the change in cardiac output per change in oxygen consumption. Twenty-seven patients were compared with 17 age-, size- and sex-matched control subjects. Patients with PR had larger right ventricles ($p \leq 0.001$), lower heart rate response ($p \leq 0.05$), lower maximal oxygen consumption ($p \leq 0.005$) and lower workloads ($p \leq 0.005$) when compared with normal control subjects during maximal exercise testing. Exercise factor was the same for both groups. Patients with PR were then separated into mild, moderate and severe groups. Patients with mild PR had a normal response to exercise. However, patients with moderate and severe PR had lower maximal oxygen consumptions and maximal workloads than control subjects. Control, mild and moderate PR groups had similar exercise factors. Patients with severe PR had markedly low cardiac output responses. PR is associated with reduced exercise capability, which is related to the severity of the PR.

(Am J Cardiol 1988;61:595–601)

Pulmonary regurgitation (PR) is a common finding after surgery for critical pulmonary stenosis, tetralogy of Fallot or other defects that may require placement of a nonvalved conduit from the right ventricle to pulmonary arteries. Many of these patients have done well, but the influence of PR on exercise capacity is unknown. Inability to quantitate PR has impeded its investigation.[1] Pulsed Doppler echocardiography has recently been shown to accurately measure regurgitant fraction.[2] Magnitude of Doppler regurgitant fraction has compared well to clinical determinants of disease severity.[2] This study was designed to determine the hemodynamic responses to exercise in postoperative patients with PR using Doppler-measured regurgitant fraction to indicate severity of the PR.

Methods

Patient selection: Thirty-one patients with postoperative PR were chosen for study. Patients were at least 6 years of age and able to perform rigorous exercise testing. Patients were excluded if they had Doppler echocardiographic or catheterization findings of residual shunts, aortic, mitral or tricuspid regurgitation, stenosis or some combination of these. Patients with right ventricular outflow tract gradients >20 mm Hg, excluding peripheral stenosis, also were excluded. All patients had to be in sinus rhythm during exercise. An age- and sex-matched control group was also studied. Consent was obtained according to the guidelines of the University of Arizona Human Subjects Committee under an approved protocol.

From the Department of Pediatrics (Cardiology), University of Arizona, Health Sciences Center, Tucson, Arizona. This study was supported by a grant-in-aid from the American Heart Association, Arizona Affiliate. Manuscript received August 10, 1987; revised manuscript received and accepted October 28, 1987.

Address for reprints: Gerald R. Marx, MD, Department of Pediatrics, University of Arizona, Health Sciences Center, Tucson, Arizona 85724.

Doppler echocardiography technique: Standard 2-dimensional pulsed and continuous-wave Doppler echocardiograms (BioSound ND 2600) were performed at rest on all subjects. M-mode scans for measurement of cavity size and wall thickness were obtained with cursor alignment guided by 2-dimensional imaging. Two-dimensional images of the left and right ventricles were obtained from a short-axis parasternal plane at the level of the mitral valve chordae tendinae. The M-mode cursor was placed through the right and left ventricles perpendicular to the ventricular septum. The site of ventricular septal patch placement was avoided in patients who had surgical ventricular septal defect closure. Right and left ventricular end-diastolic dimensions, left ventricular end-systolic dimensions and left ventricular percent fractional shortening were calculated according to standard guidelines of the American Society of Echocardiography.[3] All valves and right ventricular outflow tracts were interrogated by standard Doppler echocardiographic techniques for stenosis and regurgitation.[4,5] Regurgitation was considered insignificant if retrograde velocities were mapped only in a small area immediately proximal to the valves.[4,5]

Pulmonary regurgitant fraction was measured by a previously reported pulsed Doppler technique.[2] Pulmonary forward and regurgitant velocities were obtained proximal to the bifurcation in the midpulmonary artery, right ventricular outflow tract patch or conduit. In some patients the conduit or patch was poorly visualized, and the Doppler sample volume was placed in the area of anticipated regurgitant flow. The sample volume was then maneuvered until both simultaneous negative velocities of anterograde flow and positive velocities of retrograde flow with ≤30% velocity spread were obtained (Figure 1). Modal positive and negative Doppler velocities were separately digitized over 3 beats using a dedicated software program, digitizing pad and microcomputer.[4] The program determined positive and negative mean velocity by dividing the area under the time velocity curve by distance along the time axis. Percent pulmonary regurgitation was derived as regurgitant mean velocity/forward mean velocity × 100.

Ascending aortic velocities were measured from the suprasternal notch both at rest and during 50% supine submaximal exercise for determination of average aortic acceleration and cardiac output.[6] At rest, a 3.5-MHz transducer was used to image and perform Doppler velocity interrogation. A smaller 2.25-MHz right angle transducer was used during exercise.[6]

Average aortic acceleration, averaged over 3 beats, was calculated by a previously reported method as the peak velocity divided by the time to reach peak velocity.[7,8] Aortic diameter was measured from the suprasternal notch at the sample volume site above the sinuses of Valsalva.[9] Maximal aortic diameter measured at rest was used for flow calculation during submaximal exercise. Cardiac output (ml/min) was calculated as[4,6] mean velocity (cm/min) × cross-sectional area (cm^2).

Respiratory measurements: Expired respiratory gasses were continuously collected using a Wilmore-Costill 3-way valve system.[10] Fractional concentrations of oxygen and carbon dioxide were analyzed every 30 seconds using Beckman OM-11 and Godart Capnograph rapid gas analyzers.[10] Minute ventilation was measured using a Parkinson-Cowan CD-4 gas flow meter.[10] These measurements allowed calculation of oxygen consumption, carbon dioxide production and respiratory exchange ratio.

Exercise protocol: All subjects performed a graded maximal exercise test on a supine cycle ergometer (Spectrum Mode III) according to a standard protocol.[11] Maximal exercise capacity was also determined with patients pedaling an upright cycle in 34 of 44 subjects using the same protocol. (Ten young subjects were unable to reach the pedals.) This upright test allowed calculation of relative maximal endurance index, a measure of work performed indexed for size, sex and age.[11] The technician supervising the maximal exercise testing was blinded to patient's medical history and magnitude of PR.

An additional supine cycle exercise test was performed with the workload set to a level that corresponded to 50% of each individual's previously determined maximal oxygen consumption.[6] Oxygen consumptions and Doppler cardiac outputs were mea-

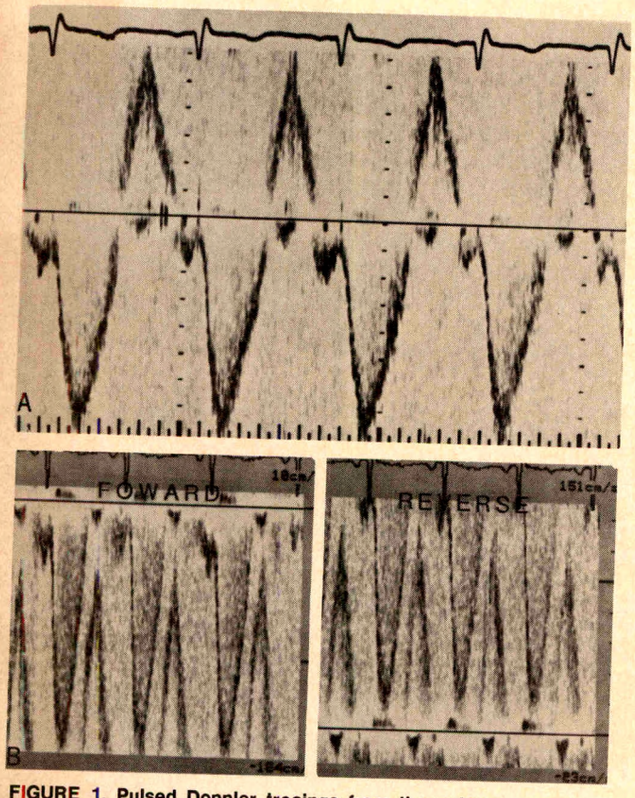

FIGURE 1. Pulsed Doppler tracings from the pulmonary outflow tract in 2 patients with pulmonary regurgitation (*A* and *B*). Anterograde, below baseline, and regurgitant, above baseline, velocities are sampled from the same flow area. *B* demonstrates baseline shift allowing simultaneous velocity measurement without signal aliasing.

TABLE I Individual Data

Group	Pt	Age (yr)	BSA (m^2)	Diag	Patch Cond.	PPS	RV/Ao	PR (%)	RVEDd LVEDd (mm/m^2)		FS (%)	R Acc Ex Acc (cm/s^2)		MHR (bpm)	$M\dot{V}O_2$	RMEI	EF
Control	62	8	1	C	C	C	C	0	22	40	30	1,558	3,189	165	30.2	111	5.9
	64	8	0.8	C	C	C	C	0	21	48	32	883	2,036	200	45.2	193	8.3
	63	9	1	C	C	C	C	0	17	43	33	840	2,071	180	43.5	192	6.8
	66	10	1	C	C	C	C	0	18	45	38	1,556	2,269	150	27	75	6.5
	65	10	1	C	C	C	C	0	*					180	35.4	150	
	61	10	1.2	C	C	C	C	0	13	35	29	1,045	1,813	150	24.8	38	8.2
	43	13	1.3	C	C	C	C	0	11	35	33	1,187	2,854	195	44.2	150	6.7
	45	13	1.3	C	C	C	C	0	13	33	35	2,340	3,575	198	45.8	210	5.3
	41	14	1.2	C	C	C	C	0	12	40	42	1,073	2,659	190	45.5	241	6.9
	47	14	1.3	C	C	C	C	0	12	34	33	967	2,048	180	40.5	174	5
	52	14	1.6	C	C	C	C	0	12	31	40	1,489	2,037				5.7
	44	14	1.3	C	C	C	C	0	9	34	36	1,546	2,645	192	43.1	193	5.3
	46	14	1.3	C	C	C	C	0	13	28	31	1,177	2,031	192	30.4	150	6.9
	42	14	1.4	C	C	C	C	0	14	34	38	1,603	2,317	195	38	168	6.5
	48	14	1.4	C	C	C	C	0	13	31	32	1,064	2,083	195	48.6	191	6.2
	51	15	1.4	C	C	C	C	0	12	36	36	2,066	2,152				5.7
	53	16	1.4	C	C	C	C	0	13	31	34	1,524	2,234	170	47.6	167	4.9
Mean		12	1.2						14	36	35	1,370	2,376	182	39	160	6.3
SD		3	0.2						3.6	5.6	3.6	421	484	17	7.9	52	1
Mild	29	7	0.7	TF	0	0	38	10	23	47	39	1,516	4,344				10.3
	23	9	1	TF	0	0	37	36	17	44	27	1,195	1,739	180	38.8	142	5.9
	25	12	1.3	TF	0	0	33	13	18	32	36				25.8	82	
	19	12	1.1	TF	0	0	34	30	29	32	34	661	1,012	168	27.2	135	6.3
	8	19	1.5	TF	0	0	45	36	20	30	33			190	39.6	158	
	9	8	0.7	PS	0	0		16	21	34	40	626	4,548				5.5
	14	13	1.4	PS	0	0		30	13	32	38	1,955	2,855	182	33.1	134	5.7
	24	14	1	PS	0	0	23	13	21	40	38	1,603	2,482	160	43.7	187	5.3
	4	16	1.6	PS	0	0		15	18	28	36	1,371	4,333	188	47.5	238	6.3
Mean		12	1.1				35	22	20	35	36	1,275	3,045	178	37	154	6.5
SD		4	0.3				7.4	10.7	4.4	6.6	4	490	1,402	12	8.2	49	1.7
Moderate	16	9	0.7	TF	P	0	33	48	43	40	29	1,254	2,422				8.3
	12	9	0.8	TF	P	0	39	43	34	35	32	935	2,429				6.1
	17	10	1.2	TF	P	0	48	44	17	32	29	757	1,315	160	28.1	37	6.2
	27	15	1.4	TF	P	0		44	25	26	38	1,151	1,477	190	25.1	84	9.8
	15	17	1.4	TF	P	0	40	51	26	22	32	865	3,865	155	25.1	84	8.7
	10	25	1.5	TF	0	R&LPA	55	53	21	24	31			160	20.1	53	
	18	7	0.9	DORV	C	RPA	60	44	33	36	37			186	38.4	137	
	7	8	1	PS	0	0		51	20	35	29	1,266	2,863				6.8
	13	9	0.9	PS	P	0	46	46	27	34	32	1,881	4,457				7.9
	1	13	1.6	PS	0	0	32	54	18	25	25	1,273	3,158	180	28.6	86	7.4
Mean		12	1.1				44	48	26	31	31	1,173	2,748	172	28	80	7.6
SD		6	0.3				10.1	4.2	8.2	6.1	3.9	349	1,084	15	6.1	34	1.2
Severe	20	10	1	TF	C			83	30	34	32	1,243	2,539	160	29	40	4.7
	6	11	0.9	TF,PA	C	RPA	58	80	41	36	38	1,674	1,707	140	17.8	−2	4.7
	3	11	1.1	TF	C	R&LPA	100	81	38	34	37	964	816	152	24.7	−18	3.8
	22	12	1.3	TF	P			82	25	38	34	868	2,385	160	22.1	98	3.4
	26	7	0.8	TGA†	C	R&LPA	75	68	44	40	28	970	1,943				3.7
	21	7	0.9	TA	C	R&LPA	64	72	34	48	30	971	3,106				5.8
	30	9	1.1	TA	C			76	34	31	29	948	1,436	172	27.8	50	4.4
	11	11	0.9	PS	C			70	38	30	44	1,556	2,390	148	30.8	89	2.6
Mean		10	1				74	77	36	36	34	1,149	2,040	155	25	43	4
SD		2	0.2				18.7	5.9	6.1	5.8	5.4	309	718	11	4.8	47	1

bpm = beats/min; C = control; Cond = conduit; Diag = diagnosis; DORV = double-outlet right ventricle; EF = exercise factor; Ex Acc = exercise mean acceleration; FS = fractional shortening; LPA = left pulmonary artery; LVEDd = left ventricular end-diastolic dimension; MHR = maximal heart rate; $M\dot{V}O_2$ = maximal oxygen consumption; PA = pulmonary atresia; PPS = peripheral pulmonic stenosis; PR = pulmonary regurgitation; PS = pulmonic stenosis; R Acc = resting mean acceleration; RMEI = relative maximal endurance index; RPA = right pulmonary artery; RV/Ao = right ventricular/aortic pressure ratio; RVEDd = right ventricular end-diastolic dimension; SD = standard deviation; TA = truncus arteriosus; TF = tetralogy of Fallot; TGA = transportation of the great vessels; VSD = ventricular septal defect.

* = no echocardiographic data available; † = TGA, VSD and PS.

sured at rest and during the fifth minute of exercise at the predetermined workload. Exercise factor was calculated as the change in cardiac output between rest and exercise, divided by the simultaneous change in oxygen consumption.[6]

Statistical analysis: Grouped data for control and all PR subjects were compared using the unpaired Student *t* test. Data were then separated into control, mild, moderate and severe categories by magnitude of PR, according to a prior classification[2]: PR fraction <40% (mild), 40 to 60% (moderate) and >60% (severe). Statistical differences between groups were determined by analysis of variance and Scheffe post-hoc analyses. A p value of ≤ 0.05 was considered significant. Group data were expressed as mean and standard deviation.

Results

Control group versus entire pulmonary regurgitation group: Seventeen control subjects and 31 patients with PR were enrolled in the study. Four patients with PR did not meet minimal requirements for study and were excluded from the protocol, leaving 27 PR patients for data analysis (Table I). Control and PR groups were not significantly different in age, sex distribution and body surface area. Left ventricular end-diastolic dimension, percent fractional shortening and resting and exercise Doppler average aortic acceleration were not significantly different for both groups (Figure 2). The PR group had significantly larger right ventricles than control subjects ($p \leq 0.001$, Figure 2). The PR group also had significantly lower maximal heart rate response ($p \leq 0.05$), lower maximal oxygen consumption ($p \leq 0.005$) and lower workload performed during maximal exercise testing ($p \leq 0.005$, Figure 3). Exercise factor was not significantly different for both groups (Figure 3).

Control group versus mild, moderate and severe groups: *Population, age and size:* Data were then analyzed by separating subjects into mild, moderate and severe PR groups (Table I). The control group consisted of 17 subjects (mean age 12 years), mild group 9 patients (mean age 12 years), moderate group 10 patients (mean age 12 years) and severe group 8 patients (mean age 10 years). Age and size were not significantly different for all 4 groups.

Diagnoses in mild group: Five patients in the mild PR group had repair of tetralogy of Fallot. None required a transanular patch or conduit. Four patient had isolated valvar pulmonic stenosis. Three had surgical pulmonary valvotomies, and 1 patient underwent balloon dilation valvuloplasty. None of the 9 patients had significant peripheral pulmonic stenosis.

Diagnoses in moderate group: Six patients in the moderate PR group had repaired tetralogy of Fallot; 5 required a transanular patch. The 1 patient without a patch had significant bilateral peripheral pulmonic stenosis. Three patients had pulmonary valvotomies in the newborn period for critical valvar pulmonic stenosis; 2 required a second operation. One had a repeat valvotomy, and the other placement of a transanular patch. One patient had a nonvalved conduit after Damas-Stansel-Kaye repair for double-outlet right ventricle.

Diagnoses in severe group: Seven patients in the severe PR group had nonvalve conduits. Four of the 7 underwent recent cardiac catheterizations and all 4 had significant peripheral pulmonic stenosis. The eighth patient had transanular patch repair for tetralogy of Fallot and has not undergone postoperative catheterization.

Baseline data: *Magnitude of regurgitation:* Mean PR fraction was 22% (10.7 standard deviation [SD]) for the mild group; 48% (4.2 SD) for the moderate group; and 77% (5.9 SD) for the severe group, ($p \leq 0.001$). All 3 groups were significantly different from each other.

Right ventricle-to-aortic pressure ratio: Cardiac catheterization data were retrospectively reviewed for calculation of right ventricular-to-aortic pressure ratio in 18 (67%) patients. Mean right ventricular-to-aortic pressure ratio was 35% (7.4 SD) for the mild group (n = 6); 44% (10.1 SD) for the moderate group (n = 8); and

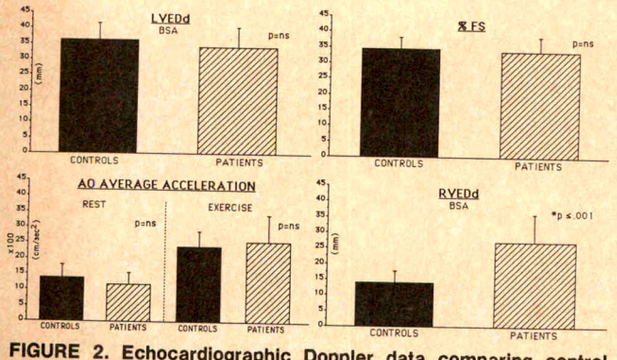

FIGURE 2. Echocardiographic Doppler data comparing control group versus entire pulmonary regurgitation group. Left ventricular end-diastolic dimension (LVEDd), left ventricular percent fractional shortening (%FS) and Doppler aortic (Ao) average acceleration at rest and exercise was similar for both groups. Patients had significantly larger right ventricular end-diastolic dimensions (RVEDd).

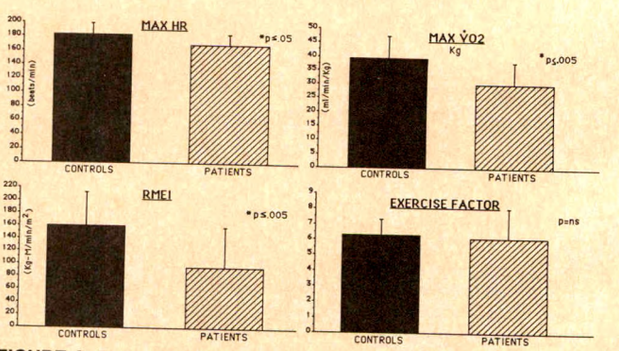

FIGURE 3. Exercise hemodynamics comparing control group with entire pulmonary regurgitation group. During maximal upright cycle ergometry patients had lower maximal heart rate (Max HR), oxygen consumption (max$\dot{V}O_2$) and workload (RMEI) than the control group. Exercise factor measured during submaximal exercise was not significantly different.

74% (18.7 SD) for the severe group (n = 4), ($p \leq 0.001$). The severe group was significantly different from both mild and moderate PR groups; the latter 2 groups were not significantly different from each other.

M-mode data: Mean left ventricular end-diastolic dimension indexed for body surface area and percent fractional shortening were not significantly different for the 4 groups (Figure 4). Mean right ventricular end-diastolic dimension was 14 mm/m^2 (3.6 SD) for the control group; 20 mm/m^2 (4.4 SD) for the mild group; 26 mm/m^2 (8.2 SD) for the moderate group; and 36 mm/m^2 (6.1 SD) for the severe group ($p \leq 0.001$). All groups were significantly different from each other (Figure 4).

Aortic average acceleration: Average resting and exercise aortic accelerations were not significantly different for all 4 groups (Figure 4).

Exercise data: Not all patients were tall enough to reach the pedals of the upright cycle ergometer. Comparison of maximal upright cycle testing data was made in 15 patients in the control group, 7 in the mild, 6 in the moderate and 6 in the severe PR groups.

Maximal heart rate: Mean maximal heart rate attained for the control group was 182 beats/min (17 SD); 178 (12 SD) for the mild group, 172 (15 SD) for the moderate group and 155 (11 SD) for the severe PR group ($p \leq 0.01$). Only the control and severe groups were significantly different from each other (Figure 5).

Maximal oxygen consumption: Mean maximal oxygen consumption was 39 ml/min/kg (7.9 SD) for the control group, 37 (8.2 SD) for the mild group, 28 (6.1 SD) for the moderate group and 25 (4.8 SD) for the severe PR group ($p \leq 0.005$). Both the moderate and severe groups were significantly different from control. The severe group was also significantly different from the mild group (Figure 5).

Relative maximal endurance index: Mean relative maximal endurance index for the control group was 160 kg-m/min/m^2 (52 SD), 154 (49 SD) for the mild group, 80 (34 SD) for the moderate and 43 (47 SD) for the severe group ($p \leq 0.001$). Both moderate and severe PR groups were significantly different from the control group (Figure 5).

Exercise factor: Mean exercise factor for the control group was 6.3 (1.0 SD), 6.5 (1.7) for the mild group, 7.6 (1.2) for the moderate group and 4.1 (1.0 SD) for the severe PR group ($p \leq 0.001$). The severe group was significantly different from the other 3 groups (Figure 5).

Discussion

Results of this study demonstrated that subjects with PR had lower maximal heart rate responses, lower maximal oxygen consumptions and lower maximal workload capacities during upright bicycle ergometry compared with normal control subjects. In addition, the magnitude of response was related to the degree of PR. Subjects with mild PR had normal hemodynamic responses to exercise. Subjects with moderate and severe PR had lower maximal oxygen consumptions and maximal workload capacities. Control, mild and moderate PR groups had similar increases in cardiac output per increase in oxygen consumption during submaximal exercise. However, some patients in the severe group had a markedly low cardiac output response. Patients with more severe PR had increased M-mode right ventricular end-diastolic dimensions. Right ventricular systolic pressures were increased at catheterization. The most severe PR occurred in patients who had pulmonary artery stenosis distal to their patches or nonvalved conduits.

Results of this study are consistent with those of others who have reported increased right ventricular size,[12] reduced radionuclide right ventricular ejection fraction[12] and decreased exercise capacity[13] in pa-

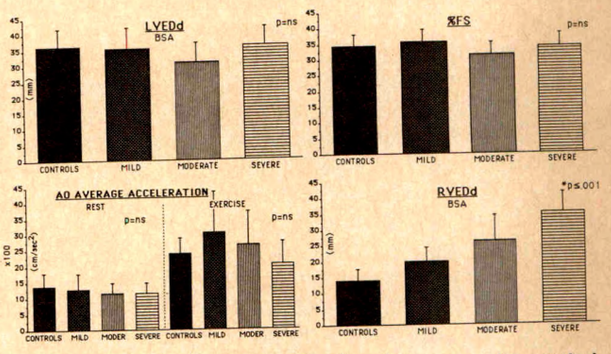

FIGURE 4. Echocardiographic Doppler data comparing control, mild, moderate and severe pulmonary regurgitation groups. Analysis of variance p values are shown in *upper right* of each panel. Left ventricular end-diastolic dimension (LVEDd); left ventricular percent fractional shortening (%FS) and Doppler aortic (Ao) average acceleration at rest and exercise were not significantly different for all groups. Right ventricular end-diastolic dimension was increased in relation to percent pulmonary regurgitation.

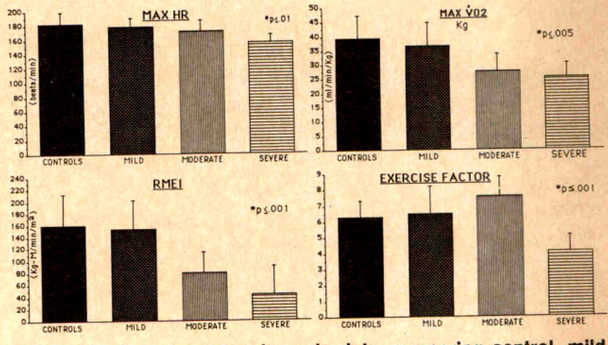

FIGURE 5. Exercise hemodynamic data comparing control, mild, moderate and severe pulmonary regurgitation groups. Analysis of variance p values are shown in *upper right* of each panel. During maximal upright cycle ergometry the severe group and lower maximal heart rate than controls. Moderate and severe groups had lower maximal oxygen consumption (Max $\dot{V}O_2$) than the control group; the severe group was also lower than the mild group. Moderate and severe groups had lower workload (RMEI) than the control group. The severe group had lower exercise factor during submaximal exercise than each of the other 3 groups.

tients with PR. Additionally, reduction in right ventricular size,[14,15] improved right ventricular function[14,15] and exercise capacity[14,15] and improvement in clinical findings of right heart failure[15,16] have been reported after pulmonary valve placement for severe PR. However, other investigators[17] have reported low exercise factor in postoperative tetralogy of Fallot patients regardless of the absence or presence of a pulmonary valve.

In this study Doppler measurement of percent PR assumed a constant diameter throughout the cardiac cycle. A previous study confirms the validity of this premise.[2] This calculation also appears valid in 15 of 27 subjects (56%) who had outflow tract patches or conduits. Nonetheless, the intent of this study was not to use measurement of Doppler PR fraction in absolute terms, but rather to separate subjects into broad categories of mild, moderate and severe PR.

M-mode-derived left ventricular end-diastolic dimensions and percent fractional shortening were not significantly different for all 4 groups. However, right ventricular volume overload causing paradoxical septal wall motion[18] and ventricular septal defect patches make absolute measurement of ventricular size difficult. Hence, reliance on comparison between groups of patients, and not on absolute values for ventricular size, is emphasized. In addition, percent fractional shortening has limitations as a determinant of ventricular function since it is both pre- and afterload dependent. An index for noninvasive measurement of ventricular function has been reported that is preload independent, incorporates afterload and is heart rate corrected. This index is the end-systolic wall stress/heart rate corrected velocity of fiber shortening relation.[19] Others have used this index to demonstrate that patients with conduit repair for transposition of the great arteries, ventricular septal defect and pulmonary stenosis have decreased left ventricular function.[20] Use of this index may uncover differences in left ventricular performance between pulmonary regurgitation patients.

Average aortic acceleration compares well with changes in dP/dt and dQ/dt under conditions of varying preload, heart rate and inotropic state in animals.[21] Average aortic acceleration has also been used to differentiate adult patients with myocardial dysfunction.[8] In our study, all patient groups had statistically similar average aortic accelerations at rest and at submaximal exercise, although the severe group tended to have a lower aortic acceleration during exercise.

An exercise factor of 7.2, measured at catheterization, has been reported in pediatric patients.[22] One study in normal preadolescent boys[6] measured cardiac output by pulsed Doppler during submaximal exercise and found an exercise factor of 6.4 (1.2 SD). In our study only 4 patients (all in the severe PR group) had exercise factors lower than 2 SD below the previously reported normal mean value. Two of these patients had right ventricular to aortic pressure ratios >70% at catheterization. Excessive patient motion and respiratory effort prevented obtaining adequate Doppler ascending aortic velocity traces at higher workloads. Hence, exercise factor and aortic acceleration were measured only at submaximal exercise. Measurement of exercise factor and aortic acceleration at higher workloads may have more clearly differentiated the patient groups.

Other variables, in addition to pulmonary regurgitation, may have contributed to the differences in patient groups. Patient age, age at surgery, type of repair and myocardial preservation could not be controlled between patient groups. The population was heterogeneous and included patients with different lesions. However, when we analyzed the data for tetralogy of Fallot patients alone, results were statistically similar to those for patients with other lesions.

In addition, hemodynamically significant PR did not appear to occur as an isolated event. Absence of a functional valve in the pulmonary position and elevated distal pulmonary pressure appear to be requirements for hemodynamically significant PR, regardless of the type of underlying defect. Elevated distal pulmonary pressure occurred in our study as a result of peripheral pulmonary stenosis, but presumptively could occur secondary to pulmonary parenchymal or pulmonary vascular obstructive disease. Decreased pulmonary flow to 1 or both lungs, and associated ventilation-perfusion abnormalities, may also have contributed to decreased exercise capacity.[13] As shown by catheterization data, available in two-thirds of the patients in this study, significant PR was associated with right ventricular hypertension. Decreased right ventricular ejection with exercise has been reported in patients with right ventricular hypertension from obstructed conduits alone.[23] In this study, patients with increasing severity of PR also had more right ventricular dilation. However, no direct measure of right ventricular systolic or diastolic function was made. Right ventricular dilation may have been an indicator of primary ventricular dysfunction related to large ventriculotomies for placement of noncontractile patches or conduits.[24] Additionally, the more dilated right ventricles may have adversely affected left ventricular diastolic function.[25] Similar to other investigators,[13] we do not believe that PR alone caused the abnormal response to exercise, but rather a constellation of findings associated with significant PR were the probable etiologies.

Many of our patients with moderate and severe PR were able to attend school and lead active lives. Although baseline Doppler echocardiograms demonstrated right ventricular dilation and increased regurgitant fractions, exercise testing most clearly differentiated the moderate and severe PR patients.

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Results of the Modified Fontan Operation in Adults

RICHARD A. HUMES, MD, DOUGLAS D. MAIR, MD, CO-BURN J. PORTER, MD, FRANCISCO J. PUGA, MD, HARTZELL V. SCHAFF, MD, and GORDON K. DANIELSON, MD

The results of the modified Fontan procedure were examined in 77 patients 18 years of age and older who underwent operation at this institution between October 1973 and December 1986. This series represents 16% of the patients undergoing the modified Fontan operation during that period. Of the 77 patients (46 men and 31 women), 29 had tricuspid atresia, 30 had double-inlet ventricle and 18 had other complex lesions. There were 5 (6%) hospital deaths, compared with 67 (17%) for patients of all ages undergoing the Fontan operation during the same period. Patient age 18 years and older was not a significant risk factor. There were 8 late deaths. Detailed follow-up data were available on 61 (95%) survivors from 5 months to 12 years (mean 4 years) postoperatively. Fifty-seven (93%) of the patients were in New York Heart Association class I or II, 20 (33%) were taking no medication and 11 (18%) were taking digoxin alone. Seventeen (28%) patients complained of persistent ascites or edema. The study indicated that (1) the modified Fontan operation can be performed with low mortality in adults, (2) the long-term outcome is favorable and (3) persistent ascites or edema may be a problem in some patients.

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Since the original description by Fontan and Baudet[1] in 1971 and subsequent modifications by Kreutzer et al[2] in 1973, the direct atrial-pulmonary arterial connection or Fontan operation has been used successfully to separate the pulmonary and the systemic circulations in patients who have a functional single ventricle. The results of the Fontan operation in younger patients have been examined previously. We examined the results of the modified Fontan operation in adults, specifically patients 18 years of age or older.

Methods

Patients: Between October 1, 1973, and December 31, 1986, 496 patients underwent a Fontan or modified Fontan operation at our institution. Seventy-seven of these patients (16%) were 18 years or older at the time of operation. The clinical records of these 77 patients were reviewed.

The ages of the 77 patients (46 men and 31 women) ranged from 18 to 42 years (mean 24). All patients had a cardiac catheterization performed at our institution or the referring institution before operation. The pulmonary artery pressure ranged from 8 to 44 mm Hg (mean ± standard deviation, 19.1 ± 8.5). The ventricular end-diastolic pressure ranged from 3 to 32 mm Hg (mean 13.8 ± 6.0), and the pulmonary arteriolar resistance ranged from 0.2 to 3.9 units · m^2 (mean 1.8 ± 1.0). Criteria for operability follow modified guidelines established by Choussat et al.[3] Evidence of pulmonary vascular disease (pulmonary arteriolar resistance >5.0 units · m^2) or markedly hypoplastic (not discretely stenotic) pulmonary arteries is considered to be a contraindication to a successful Fontan operation.

The patients were classified as having tricuspid atresia, double-inlet ventricle or other complex lesions (Table I)—a classification consistent with previous reports from our institution.[4,5] These anatomic variations are associated with a functional single ventricle in all patients.

Sixty-four (83%) patients had had a previous palliative procedure (Table II). The most frequent operation was a Blalock-Taussig (subclavian artery-pulmonary artery) anastomosis, and next in frequency was the Glenn (superior vena cava-pulmonary artery) procedure. Thirty patients had 1 previous operation; 28 had 2; and 6 had 3 or more.

The operative technique for the various modifications of the operation has been the subject of previous reports.[4,5] In our earliest experience, heterograft valves or valved conduits were placed in the inferior or the superior vena cava or the pulmonary artery. Such placement was done in 10 patients in our study. This technique was largely abandoned by 1980 because the valves were found to be unnecessary.

Postoperative management involved the routine use of inotropic agents such as dopamine and dobutamine. Afterload-reducing agents, such as sodium nitroprusside, were routinely used during the immediate postoperative period and were replaced with captopril (angiotensin-converting enzyme inhibitor) during the ambulatory recovery period. Digoxin, furosemide and

From the Section of Pediatric Cardiology and the Section of Thoracic and Cardiovascular Surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Manuscript received August 11, 1987; revised manuscript received October 21, 1987, and accepted October 23.

Address for reprints: Douglas D. Mair, MD, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905.

spironolactone were also routinely administered during the postoperative period. Atrial and ventricular epicardial wire electrodes were routinely placed at the time of surgery and were used for diagnostic monitoring of arrhythmias or pacing, as required.

Hospital mortality was defined as death either while in the hospital or <30 days after operation. Follow-up was obtained by direct patient contact (by telephone or in person), requesting the patient's current subjective condition, exercise tolerance, medications and ability to perform daily activities.

Results

There were 5 hospital deaths (6%). This rate is significantly less than the 17% for patients of all ages and the 19% in our entire experience for patients younger than 18 years old undergoing the Fontan operation ($p = 0.04$, Fisher's exact test). Four of the 5 deaths occurred before 1981. The hospital deaths occurred at 0 to 53 days after operation. The cause of death was sepsis in 2 patients and myocardial failure in 3 patients. There were no significant differences in preoperative pulmonary artery pressure, ventricular end-diastolic pressure, pulmonary arteriolar resistance, ventricular ejection fraction or age between operative survivors and nonsurvivors (unpaired *t* test). Hospital mortality occurred in 3 cases of double-inlet ventricle, 1 of tricuspid atresia, 1 of left atrial isomerism (polysplenia), common atrioventricular valve and anomalous systemic and pulmonary venous return. There were 8 late deaths, occurring at 33 days to 4 years (mean 2 years) postoperatively. The cause of the late deaths was myocardial failure in 3 patients, sudden death (suspected arrhythmia) in 2, and renal failure, hepatic failure and pulmonary hemorrhage in 1 each.

Four patients required replacement of the left atrioventricular valve at the time of the Fontan operation, and 2 patients underwent repair of the atrioventricular valve because of severe atrioventricular valve insufficiency. All patients who underwent valve replacement survived to be dismissed from the hospital. One patient who had valve replacement died suddenly of an unexplained cause at home >1 month postoperatively. One patient who had repair of a common atrioventricular valve died in the operating room.

One hospital death occurred, and there were 4 late deaths among adult patients receiving heterograft valves. Although valvular obstruction led to reoperation and removal of these valves in some patients, their use did not significantly affect early or late mortality.

The preoperative presence of a particular shunt or pulmonary artery band was not significantly related to mortality. None of the patients without previous operations (age range 18 to 40 years, mean 24) died while in the hospital, and to date all have survived. This finding, however, was not statistically different from that for patients who had a previous procedure. Having >1 previous operation did not significantly affect mortality. The length of hospital stay for hospital survivors ranged from 7 to 86 days (mean 21). This was no different than that for other patients of all ages during this time period.

Follow-up was obtained on 61 of 64 (95%) surviving

TABLE I Types of Anomalies in 77 Adult Patients Undergoing the Fontan Operation

Anomaly*	Pts (n)	Sex (M/F)	Age (yr) Range	Age (yr) Mean
Doublet-inlet ventricle†	30	20/10	18–40	25
A-I	1			
A-II	3			
A-III	19			
C-I	0			
C-II	5			
C-III	2			
Tricuspid atresia‡	29	14/15	18–42	23
I-A	4			
I-B	16			
I-C	3			
II-A	0			
II-B	4			
II-C	1			
III	1			
Complex	18	12/6	18–39	24
Hypoplastic right heart syndrome	2			
Common atrioventricular valve	1			
Mitral valve atresia	4			
Straddling atrioventricular valve	6			
Hypoplastic atrioventricular valve	5			
Total	77	46/31	18–42	24

* I = normal related arteries; II = dextrotransposition of the great arteries; III = levotransposition of the great arteries.
† A = outlet chamber present; C = no outlet chamber.
‡ A = pulmonary atresia; B = pulmonary stenosis; C = normal pulmonary valve.

TABLE II Previous Operations in 77 Adult Patients Undergoing the Modified Fontan Operation

Operation*	Pts (n)
Blalock-Taussig shunt	52
Glenn shunt	19
Waterston shunt	7
Potts shunt	12
Blalock-Hanlon septectomy	5
Pulmonary trunk banding	5
Other	4
None (%)	13 (17)

* Excluding balloon atrial septostomy.

TABLE III Follow-Up Data on 61 Surviving Patients after Modified Fontan Operation

Finding	Pts No.	Pts %
NYHA class I or II	57	93
Work/attend school	57	93
Taking no medication	20	33
Ascites or edema	17	28
Taking digoxin alone	11	18
Permanent pacemaker	4	7
Varicose veins	3	5

NYHA = New York Heart Association.

patients 5 months to 12 years after operation (mean 4 years) (Table III). Three patients were lost to follow-up at 3.3, 3.6 and 5.3 years after operation. Complaints of heart rhythm disorder were followed up with inquiries to the patient's local physician when the rhythm diagnosis was unknown. Fifteen patients had a supraventricular tachyarrhythmia or atrial flutter of varying cycle lengths. Five patients had a complaint of occasional or frequent palpitations caused by premature ventricular beats. Two patients had bradyarrhythmia with atrioventricular dissociation. The occurrence of arrhythmias after the Fontan operation has been the subject of a previous report. Four patients had a permanent pacemaker, and 3 patients complained of varicose veins (2 men and 1 woman). Seventeen patients (27%) had intermittent ascites or edema early postoperatively but, with the passage of time and, in some instances, diuretic and dietary intervention, this became less of a problem in most.

Discussion

Previous studies have examined the effect of younger age, usually younger than 5 years, on the outcome of the Fontan procedure. These studies suggest that mortality is higher for the younger age group than for older children. Our experience also suggests an increased mortality in the younger age group. However, factors that necessitate operation at an early age seem to affect these results adversely. Many of the younger patients referred to our institution for Fontan repair are severely symptomatic secondary to deteriorating ventricular performance from volume overload produced by large pulmonary blood flow or atrioventricular valve incompetence. The higher mortality rate for these patients is probably a result of persistent myocardial dysfunction rather than of the Fontan repair itself.

For the adult patient with a single ventricle anomaly, the grim predictions regarding longevity made at the time of birth in the 1960s or earlier have not been realized. Many of these patients were told in their early years that nothing beyond palliation by shunts or banding would be available. Some of these patients have become productive wage earners, living well-adjusted, although perhaps sedentary, lives. The older patient who is reasonably well compensated and has become somewhat more independent in his or her lifestyle may be reluctant to consider a major surgical procedure in which the outcome is uncertain.

We present the early results of the Fontan operation in this group of patients to aid in the difficult decision of whether to consider a more definitive type of operation in these patients. Our goal in performing the Fontan procedure is to effectively reduce the ventricular volume load and to correct the arterial hypoxemia. It is hoped that this will prevent the myocardial deterioration and death in early adulthood that have characterized the natural history of these patients in the past and that the operation will increase longevity, with a reasonable and improved lifestyle. Whether the Fontan procedure will achieve these goals remains to be determined.

The hospital mortality in our group of patients was 6%. This percentage is significantly lower than that for patients younger than 18 years. Since 1980, there has been only 1 hospital death in 51 cases (2%). This rate compares favorably with a declining mortality rate for the entire group of patients undergoing the Fontan operation (10% overall, 6% tricuspid atresia, 12% double-inlet ventricle) for the same time—the more recent 5-year period. Better patient selection has been a positive influencing factor on the declining mortality rate, in addition to improved operative and postoperative management.

Arrhythmias, particularly supraventricular, may represent a significant late complication after the Fontan operation. Fifteen patients (24% of those followed up) had persistent supraventricular tachyarrhythmias. We have found that these rhythms are usually classic atrial flutter or other forms of paroxysmal atrial tachycardia. Atrioventricular block of 2:1 often occurs with these rhythms. After conversion to sinus rhythm, the initial therapy is usually digoxin and a type I antiarrhythmic agent (procainamide).

The long-term effect of elevated venous pressure on liver and gastrointestinal function, as well as on systemic veins, is unknown. Three patients complained of varicose veins in the lower extremities. This has not been a complaint of younger patients. However, the presence of this complaint may represent the combined effects of age and elevated systemic venous pressure. Despite 1 death from primary liver failure in this series, the occurrence of hepatic dysfunction is uncommon in our experience. In our series, 17 (27%) patients complained of intermittent ascites or edema, and this is a concern. Patients reported subjective improvement despite this complaint, and in most patients, this problem was well controlled by diet or diuretic medication and became less problematic with the passage of time. This seems to be a frequent complaint after the operation, and further investigation into the cause and treatment is needed.

Follow-up data suggest that most patients are doing well. The lack of need for medication and the subjective reports of improvement are encouraging. We continue to recommend that definitive exercise testing be performed on all patients who undergo the Fontan operation so that objective measures of improved performance may be recorded. A previous report from our institution has shown improved exercise tolerance after this operation.[6] As yet, too few adult patients have undergone this testing to report significant results.

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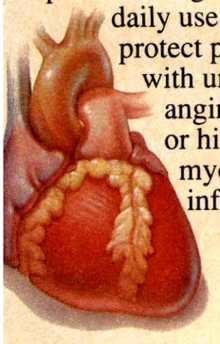

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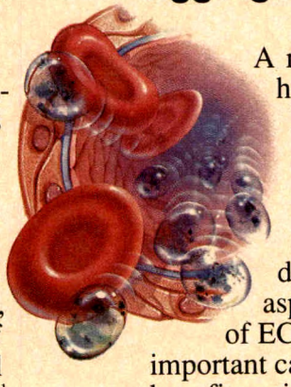

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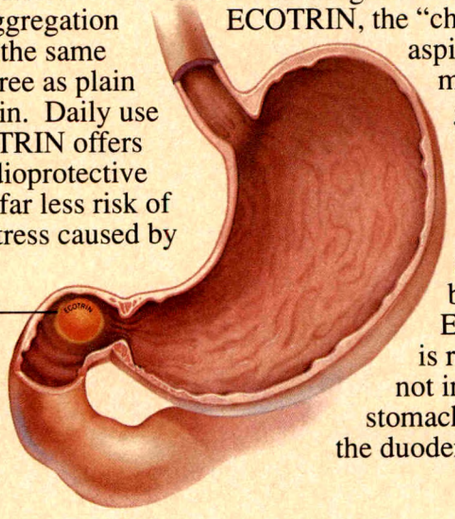

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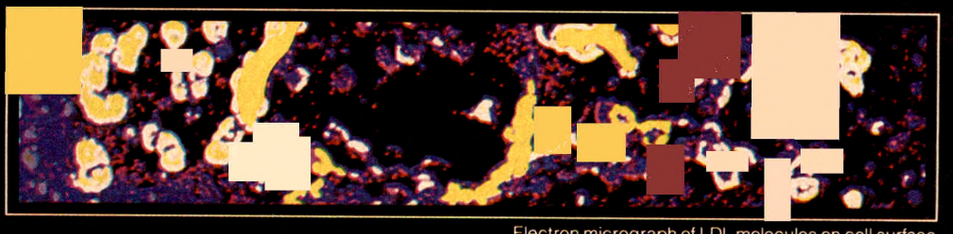

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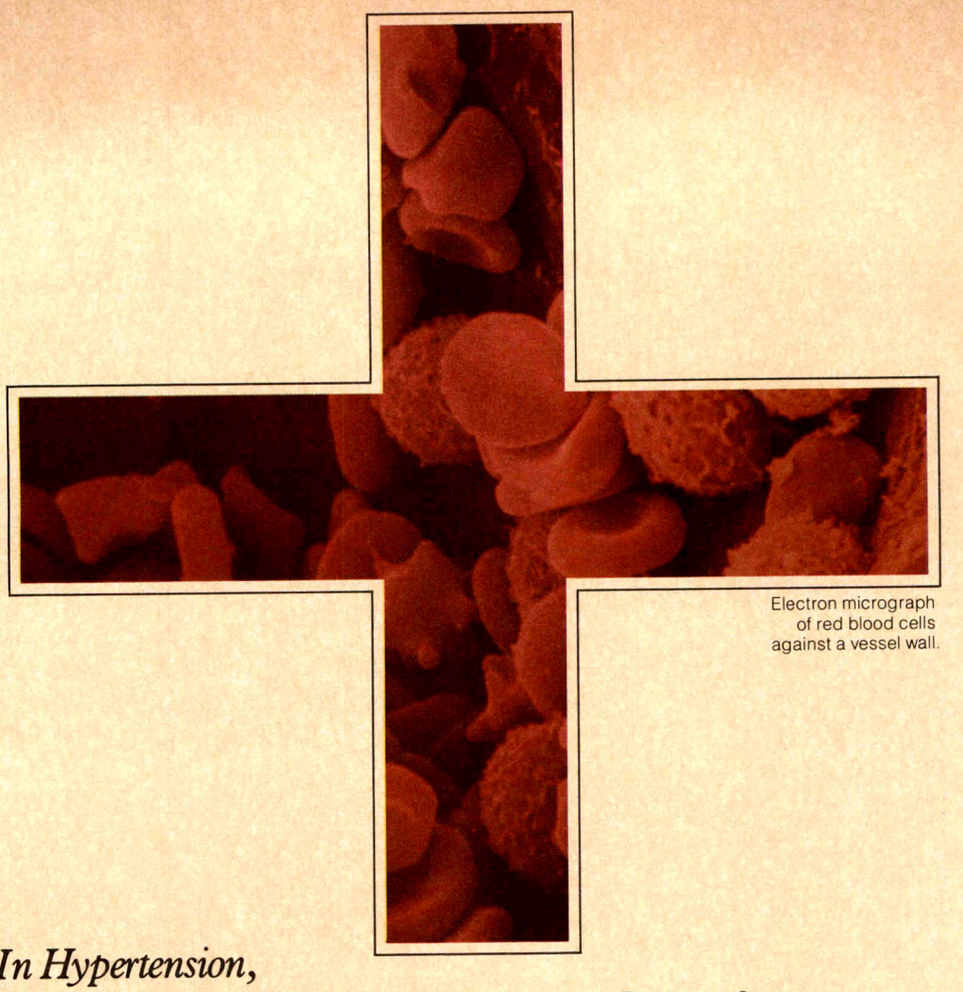

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Brief Summary
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INDICATIONS AND USAGE: MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. It is mild to moderate in activity and can be used as the initial agent or in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed.

CONTRAINDICATIONS: None known.

WARNINGS: MINIPRESS may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120–160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS. The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS therapy.

PRECAUTIONS: ***Information for Patients:*** Dizziness or drowsiness may occur after the first dose of this medicine. Avoid driving or performing hazardous tasks for the first 24 hours after taking this medicine or when the dose is increased. Dizziness, lightheadedness or fainting may occur, especially when rising from a lying or sitting position. Getting up slowly may help lessen the problem. These effects may also occur if you drink alcohol, stand for long periods of time, exercise, or if the weather is hot. While taking MINIPRESS, be careful in the amount of alcohol you drink. Also, use extra care during exercise or hot weather, or if standing for long periods. Check with your physician if you have any questions.

Drug Interactions: MINIPRESS has been administered without any adverse drug interaction in limited clinical experience to date with the following: (1) cardiac glycosides–digitalis and digoxin; (2) hypoglycemics–insulin, chlorpropamide, phenformin, tolazamide, and tolbutamide; (3) tranquilizers and sedatives–chlordiazepoxide, diazepam, and phenobarbital; (4) antigout–allopurinol, colchicine, and probenecid; (5) antiarrhythmics–procainamide, propranolol (see WARNINGS however), and quinidine; and (6) analgesics, antipyretics and anti-inflammatories–propoxyphene, aspirin, indomethacin, and phenylbutazone.

Addition of a diuretic or other antihypertensive agent to MINIPRESS has been shown to cause an additive hypotensive effect.

Drug/Laboratory Test Interactions: False positive results may occur in screening tests for pheochromocytoma in patients who are being treated with prazosin. If an elevated VMA is found, prazosin should be discontinued and the patient retested after a month.

Laboratory Tests: In clinical studies in which lipid profiles were followed, there were generally no adverse changes noted between pre- and post-treatment lipid levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenic potential was demonstrated in an 18 month study in rats with MINIPRESS (prazosin hydrochloride) at dose levels more than 225 times the usual maximum recommended human dose of 20 mg per day. MINIPRESS was not mutagenic in *in vivo* genetic toxicology studies. In a fertility and general reproductive performance study in rats, both males and females, treated with 75 mg/kg (225 times the usual maximum recommended human dose), demonstrated decreased fertility while those treated with 25 mg/kg (75 times the usual maximum recommended human dose) did not.

In chronic studies (one year or more) of MINIPRESS in rats and dogs, testicular changes consisting of atrophy and necrosis occurred at 25 mg/kg/day (75 times the usual maximum recommended human dose). No testicular changes were seen in rats or dogs at 10 mg/kg/day (30 times the usual maximum recommended human dose). In view of the testicular changes observed in animals, 105 patients on long term MINIPRESS therapy were monitored for 17-ketosteroid excretion and no changes indicating a drug effect were observed. In addition, 27 males on MINIPRESS for up to 51 months did not have changes in sperm morphology suggestive of drug effect.

Usage In Pregnancy: Pregnancy Category C. There are no adequate and well controlled studies which establish the safety of MINIPRESS (prazosin HCl) in pregnant women. MINIPRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers: MINIPRESS has been shown to be excreted in small amounts in human milk. Caution should be exercised when MINIPRESS is administered to a nursing woman.

Usage in Children: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Clinical trials were conducted on more than 900 patients. During these trials and subsequent marketing experience, the most frequent reactions associated with MINIPRESS therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

Less frequent adverse reactions which are reported to occur in 1–4% of patients are:

Gastrointestinal: vomiting, diarrhea, constipation; *Cardiovascular:* edema, orthostatic hypotension, dyspnea, syncope; *Central Nervous System:* vertigo, depression, nervousness; *Dermatologic:* rash; *Genitourinary:* urinary frequency; *EENT:* blurred vision, reddened sclera, epistaxis, dry mouth, nasal congestion.

In addition, fewer than 1% of patients have reported the following (in some instances, exact causal relationships have not been established):

Gastrointestinal: abdominal discomfort and/or pain, liver function abnormalities, pancreatitis; *Cardiovascular:* tachycardia; *Central Nervous System:* paresthesia, hallucinations; *Dermatologic:* pruritus, alopecia, lichen planus; *Genitourinary:* incontinence, impotence, priapism; *EENT:* tinnitus; *Other:* diaphoresis, fever.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported.

OVERDOSAGE: Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate MINIPRESS is not dialysable because it is protein bound.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS should be adjusted according to individual blood pressure response.

Initial Dose: 1 mg two or three times a day.

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

Revised November 1986

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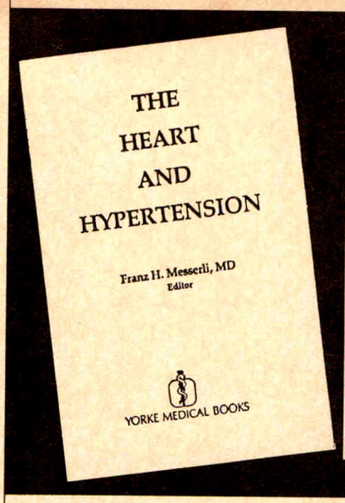

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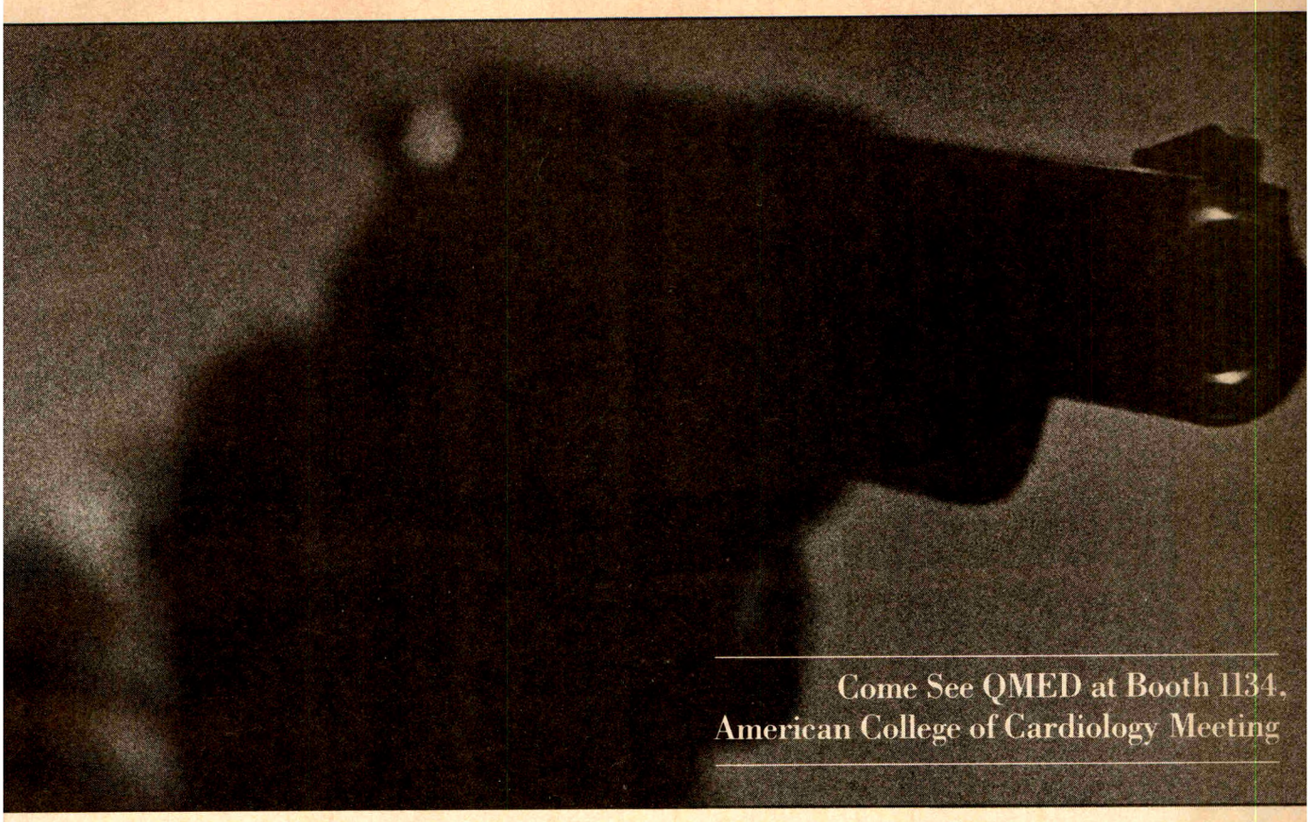

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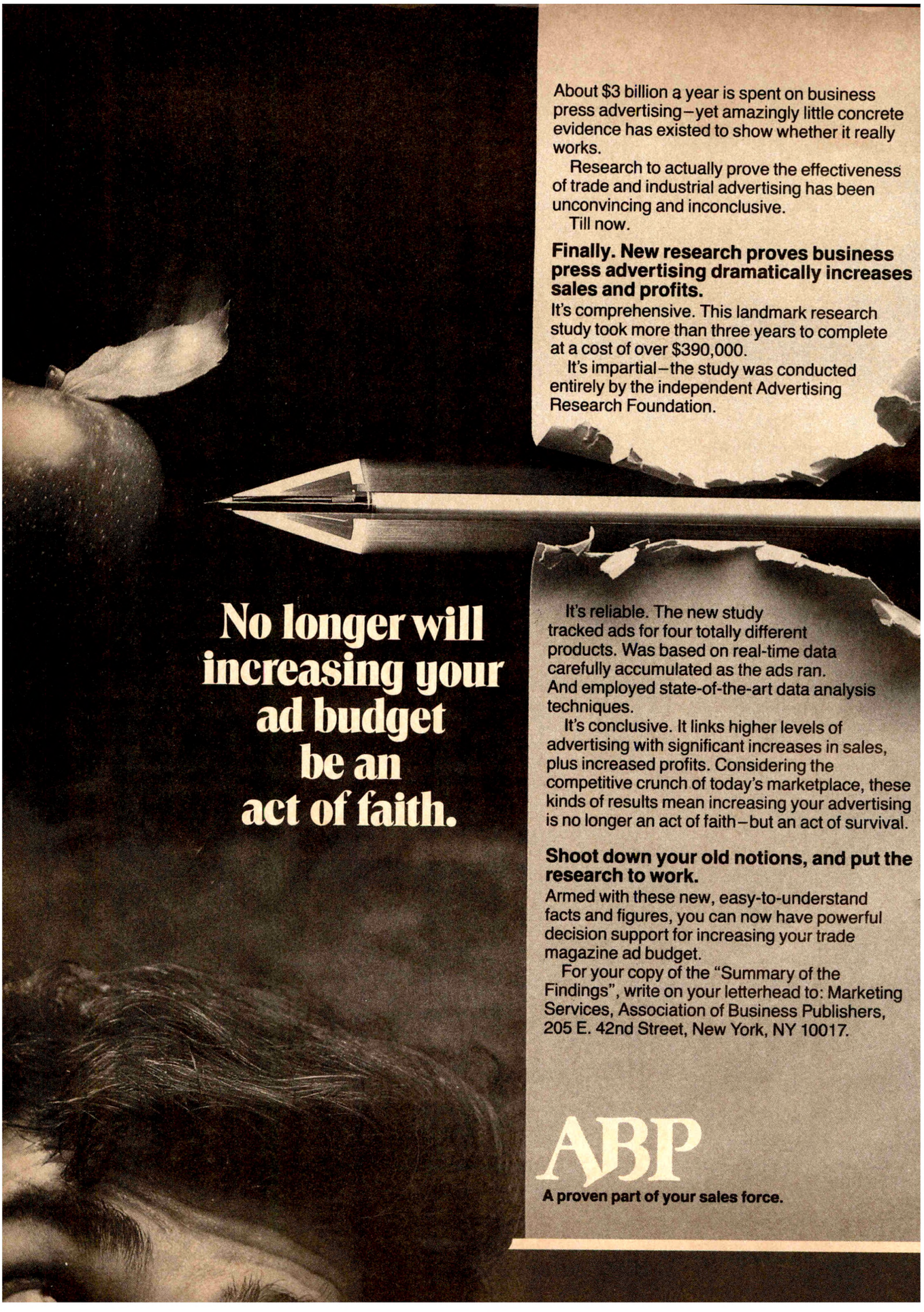

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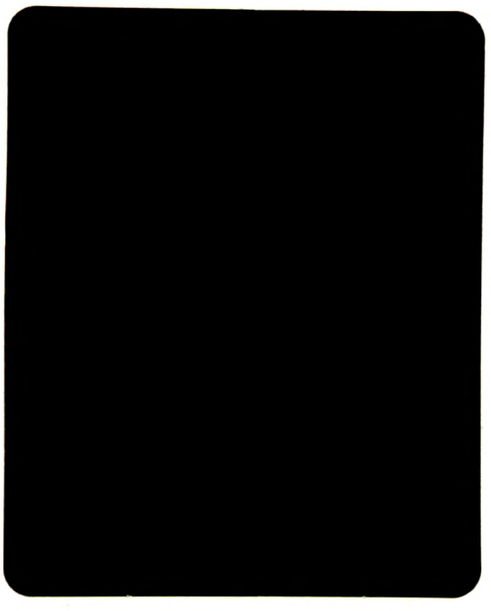

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Although to a lesser degree than aspirin, even OTC ibuprofen can cause erosions, ulcerations, and submucosal hemorrhage.

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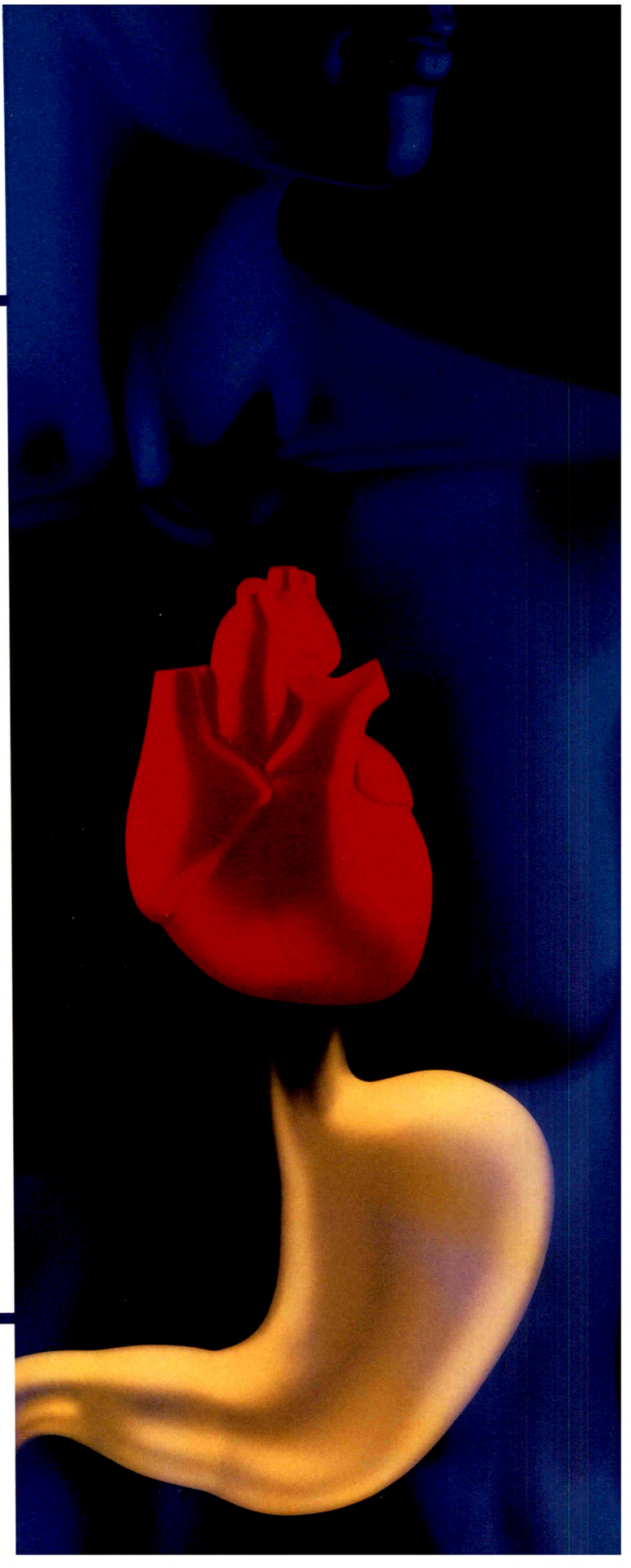
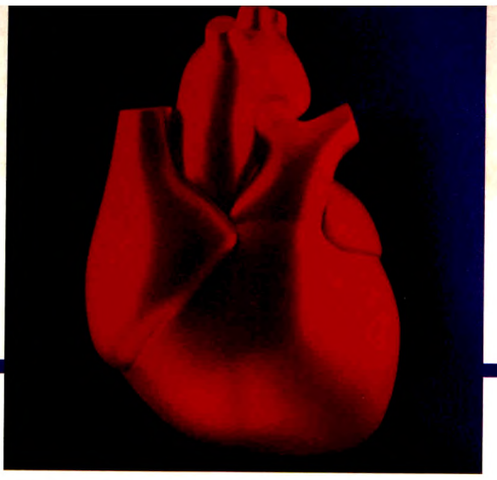
that won't interfere with the antiplatelet effects of low-dose aspirin therapy.

Another important consideration for MI/TIA patients: Extra-Strength TYLENOL® won't influence the desired antiplatelet effects of low-dose aspirin, so antiplatelet therapy won't be affected.[12,13]

Reduce the risk of compromised therapy due to simple analgesia. When you recommend low-dose aspirin for MI/TIA patients, you may wish to advise them against taking additional aspirin for simple pain relief. Specify the logical choice: Extra-Strength TYLENOL®.





Why risk compromising therapy for the sake of simple analgesia?

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For mild-to-moderate pain relief:

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- No OTC analgesic is more effective for mild-to-moderate pain
- Little risk of GI irritation
- Does not interfere with antiplatelet effects

First choice for mild-to-moderate pain relief in patients on low-dose aspirin therapy

References: 1. Multicenter study indicates one aspirin can do the job of four in preventing stroke. *JAMA* 1987;257:2134-2135. **2.** Why a little aspirin is better than a lot. *JAMA* 1987;257:2135. **3.** Aspirin after myocardial infarction. *Lancet* 1980;I:1172-1173. **4.** De Caterina R, et al: *Eur Heart J* 1985;6:409-417. **5.** Ivey KJ: *Advances in Therapy* 1984;1:190-206. **6.** Hoftiezer JW, et al: *Gut* 1982;23:692-697. **7.** Graham DY, Smith JL: *Ann Intern Med* 1986;104:390-398. **8.** Mehlisch DR, Frakes LA: *Clin Ther* 1985;7(1):89-97. **9.** Cooper SA: *Arch Intern Med* 1981;141:282-285. **10.** Data on file, McNeil Consumer Products Company. **11.** Amadio P, Jr: *Am J Med*, September 10, 1984, pp 17-26. **12.** Aspirin or paracetamol? *Lancet* 1981;II:287-289. **13.** Mielke CH, et al: *JAMA* 1976;235:613-616.

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Effect of Iron Deficiency on Tissue Oxygen Delivery in Cyanotic Congenital Heart Disease

SAMUEL S. GIDDING, MD, and JAMES A. STOCKMAN III, MD

To test the hypothesis that tissue oxygen delivery would be affected by diminished oxygen stores in cyanotic congenital heart disease, serum ferritin, transferrin saturation, hemoglobin, red cell mean corpuscular volume (MCV), red cell 2,3-diphosphoglycerate (DPG), P50, blood gases, oxygen saturations and systemic oxygen transport were measured in 29 hypoxemic infants and children. For the group, aortic saturation was 81 ± 9%, PaO_2 was 50 ± 12 mm Hg, hemoglobin 16.2 ± 2.1 gm/dl and systemic oxygen transport 620 ± 145 ml/min/m^2. P50 was increased above normal values (28.8 ± 2.3 vs 26.6 ± 1.1 mm Hg, p <0.01), and DPG was 2.35 ± 0.54 μmol/ml, at the upper limits of normal for this assay. Iron deficiency was present in 8. When patients with P50 ≥30 mm Hg and P50 <30 mm Hg were compared, iron stores were diminished in the high P50 group: [serum ferritin (19 ± 8 vs 53 ± 48 ng/ml, p = 0.0006), transferrin saturation (11 ± 6 vs 23 ± 11%, p = 0.003) and MCV (79 ± 8 vs 86 ± 4 fl, p = 0.05)]. Hemoglobin, aortic oxygen saturation, PaO_2 and systemic oxygen transport were similar in both groups. In children with iron sufficiency, 15 of 21 had MCV >90th percentile for age and sex (p <0.001 versus expected distribution). Also, MCV >90th percentile for age and sex had a positive predictive value of 0.88 for iron sufficiency. This study demonstrates that diminished iron stores in cyanotic congenital heart disease are associated with a more right-shifted oxyhemoglobin dissociation curve (increased P50). In addition, MCV was larger than in normal patients and, if >90th percentile for age and sex, suggested iron sufficiency.

(Am J Cardiol 1988;61:605–607)

An important goal in the management of cyanotic congenital heart disease is to provide adequate tissue oxygen delivery despite chronic hypoxemia. Many cyanotic patients are managed by palliative surgical and catheterization procedures that raise systemic arterial oxygen tension so that physiologic compensation through polycythemia and rightward shifting of the oxyhemoglobin dissociation curve can occur.[1-3] Recent studies have shown that patients with cyanotic congenital heart disease alter their cardiac index, hemoglobin concentration and oxyhemoglobin dissociation curve to maintain a level of systemic oxygen transport similar to that of acyanotic patients.[4]

From the Division of Cardiology, The Children's Memorial Hospital, Department of Pediatrics, Northwestern University Medical School, Chicago, Illinois. This study was supported in part by the Robert and Mary Wood Research Fellowship Grant. Manuscript received July 2, 1987; revised manuscript received and accepted October 26, 1987.

Address for reprints: Samuel S. Gidding, MD, Division of Cardiology, Children's Memorial Hospital, 2300 Children's Plaza, Chicago, Illinois 60201.

We hypothesized that tissue oxygen delivery would be adversely affected by decreased iron stores in cyanotic congenital heart disease because of an adverse effect on hemoglobin production.[5] Tissue oxygen delivery was defined as abnormal if the oxyhemoglobin dissociation curve was right-shifted in the presence of normal cardiac index, pH and temperature. To test this hypothesis we assessed tissue oxygen delivery and iron storage variables in 29 children undergoing cardiac catheterization.

Methods

Infants and children undergoing elective cardiac catheterization for cyanotic congenital heart disease were studied. Specifically excluded from the protocol were critically ill children, those <3 months of age, or with Down syndrome, which is associated with increased red cell mean corpuscular volume (MCV).[6] All parents gave consent for the study according to an institutionally approved form.

Hemoglobin and MCV were measured before cardiac catheterization (Coulter counter). At catheterization, blood was drawn for arterial blood gases (Radiometer Copenhagen ABL 30), measured aortic and

TABLE I Laboratory Data for All Patients

	Mean ± SD	Range
Aortic saturation (%)	81 ± 9	50–91
PaO_2 (mm Hg)	50 ± 12	30–70
Hemoglobin (g/dl)	16.2 ± 2.1	12.2–22.1
MCV (fl)	85 ± 6	64–98
Ferritin (ng/ml)	44 ± 43	5–175
Transferrin saturation (%)	19 ± 11	4–48
Systemic O_2 transport (ml/min/m^2)	620 ± 145	375–1018
P50 (mm Hg)	28.8 ± 2.3	25.5–33.9
Red cell 2,3-DPG (μmol/ml)	2.35 ± 0.54	1.58–4.17

DPG = diphosphoglycerate; MCV = mean corpuscular volume; SD = standard deviation.

TABLE II Iron Storage Variables

Variable	P50 ≥30 mm Hg	P50 <30 mm Hg	p Value
Ferritin (ng/ml)	19 ± 8	53 ± 48	0.006
Transferrin saturation (%)	11 ± 6	23 ± 11	0.003
MCV (fl)	79 ± 8	86 ± 4	0.05
Hemoglobin (g/dl)	16.5 ± 2.1	16.3 ± 2.1	0.84

MCV = mean corpuscular volume.

TABLE III Oxygen Delivery Variables

Variable	P50 ≥30 mm Hg	P50 <30 mm Hg	p Value
Aortic saturation (%)	75 ± 13	83 ± 7	0.15
PaO_2 (mm Hg)	45 ± 13	52 ± 12	0.19
Systemic O_2 transport (ml/min/m^2)	613 ± 101	623 ± 169	0.87
Red cell 2,3-DPG (μmol/ml)	2.76 ± 0.74	2.17 ± 0.31	0.07

DPG = diphosphoglycerate.

mixed venous oxygen saturations (American Optical Unistat Oximeter), P50 (Hemoxanalyzer), red blood cell 2,3-diphosphoglycerate (DPG) (Sigma Diagnostics Kit), fetal hemoglobin, serum ferritin, serum iron and total iron binding capacity. Oxygen consumption was measured using a flow-through hood (Waters Instruments, MRM-2) in 22 children.

Calculated variables included transferrin saturation; oxygen carrying capacity; cardiac index (Fick principle); systemic oxygen transport (arterial O_2 content × cardiac index); P50 in vivo, which was calculated using measured pH and a mathematical description of the Bohr effect ($\Delta \log P50 = -0.37\ [\Delta pH]$);[7] and DPG corrected for fetal hemoglobin concentration ([DPG, observed] × [100 − % hemoglobin F] = DPG functional).[8] Values of P50 and DPG reported were corrected for pH and hemoglobin F concentration by the above equations. Iron deficiency was defined as present if 1 or more of the following were noted: serum ferritin ≤12 ng/ml, transferrin saturation ≤7% in children <2 years of age or ≤16% in children >2 years of age, red cell MCV ≤5th percentile for age and sex in the absence of thalassemia syndrome or serum iron <50 mg/dl if total iron binding capacity was not available.[9]

Statistical analysis: Means and standard deviations were performed on all variables for the group as a whole. Patients were then divided into 2 groups: those with right-shifted oxyhemoglobin dissociation curves (P50 ≥30 torr) and those with lower P50 values. Groups were compared using an unpaired *t* test, with $p < 0.05$ for a 2-tailed test considered statistically significant. Data are presented as mean ± standard deviation.

To assess the reliability of MCV as a predictor of iron sufficiency, MCV was expressed as a percentile for age and sex.[10] The distribution of MCV in the iron-sufficient population was compared with the expected normal distribution in the population by chi-square analysis. The sensitivity, specificity and predictive value of MCV criteria for iron sufficiency for the study population were calculated.

Results

Twenty-nine patients (18 boys, 11 girls) were enrolled in the study. Mean age was 2.9 ± 2.3 years and mean weight was 13.6 ± 9.1 kg. Diagnoses included complete transposition in 9, tetralogy of Fallot in 9, other forms of right ventricular outflow tract obstruction in 5 and complex anomalies in 6.

Baseline study variables for the group as a whole are presented in Table I. The patients had significant hypoxemia and polycythemia. Of the 29 patients, 26 had hemoglobin concentration >97th percentile for age and sex, 2 were between the 90th and 97th percentiles and 1 was 50th percentile.[9] MCV was increased above normal values reported for age and sex. The oxyhemoglobin dissociation curve was right-shifted as demonstrated by increased values for P50 (28.8 ± 2.3 vs 26.6 ± 1.1 mm Hg, $p < 0.01$ vs normal values for our laboratory). Iron deficiency was diagnosed in 8 patients: low serum ferritin in 3, low transferrin saturation in 3, low transferrin saturation and low MCV in 1, and low serum ferritin, transferrin saturation and MCV in 1.

Tables II and III compare iron storage oxygen delivery variables after patients had been subdivided according to the degree of the rightward shift in the oxyhemoglobin dissociation curve. Age was similar in these groups (2.9 ± 1.8 years, P50 ≥30 mm Hg vs 3.7 ± 3.2 years, P50 <30 mm Hg). Although hemoglobin concentration was similar in both groups, children with elevated P50 had significantly lower serum ferritin, transferrin saturation and MCV. The difference in DPG approached (but did not achieve) a statistical difference. Neither aortic saturation nor PaO_2 were statistically different.

An interesting finding was an unusual distribution of MCV in our study population. In iron-sufficient children, MCV was >90th percentile for age and sex in 15 of 21 ($p < 0.001$ vs expected distribution), whereas only 2 of 8 iron-deficient children had MCV >90th percentile. The presence of an MCV >90th percentile was a good test of iron sufficiency (positive predictive value = 0.88), but its absence did not necessarily indicate iron deficiency (negative predictive value = 0.50).

An MCV <3rd percentile for age and sex was found in 2 patients in our series, 1 had a low serum ferritin and the other a low transferrin saturation. Patients treated for iron deficiency in this series had increases in MCV >90th percentile for age and sex.

Discussion

The principal finding was that diminished iron stores affected tissue O_2 delivery in cyanotic congenital heart disease. A significantly right-shift oxyhemoglobin dissociation curve in our patient population represented physiologic compensation for both chronic hypoxemia and relative anemia. The presence of P50 >30 mm Hg in a patient with chronic hypoxemia suggested the possible presence of iron deficiency, even if the patient had mild to moderate polycythemia.

Our study identified a useful marker for iron sufficiency (MCV >90th percentile for age and sex). Although not as specific as serum ferritin, this measurement is useful in confirming the presence of iron sufficiency. If the MCV is <90th percentile for age and sex, further assessment of iron stores is appropriate. In our experience, which also encompasses patients not included in this study, an MCV <3rd percentile for age and sex has been uniformly associated with severe iron deficiency or thalassemia syndrome.

We do not have a good explanation for the elevation of MCV in hypoxemic patients. MCV is known to be elevated in newborn infants, patients with folate or B_{12} deficiency, Down syndrome, hypothyroidism, liver disease, reticulocytosis and chronic obstructive pulmonary disease.[10] Oldag et al[11] noted this phenomenon in cyanotic congenital heart disease and concluded that neither an increased number of reticulocytes nor a shorted red cell survival were responsible for the increase in red cell size. It seems unlikely that either folate or B_{12} deficiency existed in our study population.[12] Another hypothesis to consider is a resumption of fetal forms of erythropoiesis, although fetal hemoglobin concentrations were within normal limits with the exception of 1 patient who was born prematurely.

The clinical importance of iron deficiency in cyanotic congenital heart disease has been emphasized in several studies. Cerebrovascular accidents in younger cyanotic children occur much more commonly in the setting of relative anemia than with severe polycythemia.[13,14] Linderkamp et al[15] showed that iron-deficient cells are less deformable and actually increase blood viscosity despite the presence of a lower hemoglobin concentration. In recent assessments of serum erythropoietin titer in patients with cyanotic congenital heart disease, several patients with low serum ferritin concentrations were identified and shown to have a tendency toward elevated erythropoietin titers suggestive of relative anemia.[16,17]

Berman et al[4] studied systemic oxygen transport in a large cohort of patients with congenital heart disease. These investigators concluded that P50, DPG and hemoglobin concentration fluctuate to stabilize arterial oxygen content. Cardiac index is then the major determinant of systemic oxygen transport. Our data would support this conclusion because systemic oxygen transport was similar among the higher and lower P50 groups. If we consider that hypoxemic iron-deficient patients may have lower hemoglobin concentrations than are appropriate and that compensatory mechanisms work to normalize systemic oxygen transport, the cost of iron deficiency may include increased resting cardiac index, right shifted oxyhemoglobin dissociation curve and lower mixed venous oxygen content.

Acknowledgment: We wish to thank Eric Valcourt for technical assistance and Shann Bulger for help in preparing the manuscript.

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Surgical Risk Factors in Total Anomalous Pulmonary Venous Connection

CHRISTOPHER R. LINCOLN, FRCS, MICHAEL L. RIGBY, MD, CORRADO MERCANTI, MD, MOHAMMAD AL-FAGIH, FRCS, MICHAEL C. JOSEPH, MD, GRAHAM A. MILLER, MD, and ELLIOTT A. SHINEBOURNE, MD

Eighty-three patients underwent surgical correction of total anomalous pulmonary venous connection (TAPVC) between 1973 and 1986. There were 46 boys and 37 girls. Median age at operation was 60 days (1 to 240) and median weight 3.9 kg (1 to 22). The anatomic types encountered included infracardiac connection (16 patients), supracardiac connection (32) and pulmonary venous drainage connected directly to the coronary sinus (27). Mixed anomalous drainage or pulmonary venous return connected directly to the right atrium occurred in 8 patients. Diagnosis was established by cardiac catheterization and angiography (56 patients), clinical examination (3) and cross-sectional echocardiography alone in 24 of the last consecutive 28 patients. Pulmonary hypertension was present in 26 (55%) of those who underwent cardiac catheterization. The median pulmonary vascular resistance was 4.2 units/m^2 (body surface area) for all the patients, whereas in those with infracardiac pulmonary venous connection the median value was 10 units/m^2. The median interval between admission and operation was 72 hours. Surgical correction was performed using profound hypothermia and circulatory arrest in 68; for the remainder, conventional cardiopulmonary bypass with profound to moderate hypothermia was used. Ten patients developed 1 or more pulmonary hypertensive crises during the early postoperative period. These were diagnosed in 8 by direct pulmonary artery pressure measurement and in 2 by clinical examination. Late reoperation was necessary in 6 patients (10%). Analyses of risk factors for 30-day survival for all patients showed that the risk of early death was associated with the type of anomaly (infradiaphragmatic), occurrence of pulmonary hypertensive crises, year of the operation, sex of the patient and presence of preoperative congestive heart failure. The risk of early death was decreased when the method of diagnosis was cross-sectional echocardiography alone. The 30-day hospital mortality from 1975 to the present was 8.5%. Six patients (10%) died later than expected. Actuarial survival of patients with infradiaphragmatic drainage was 60% at 72 months and the remainder had an 88% survival at 80 months. The whole group had an actuarial survival of 75% at 84 months.

(Am J Cardiol 1988;61:608–611)

Successful surgical correction of total anomalous pulmonary venous connection (TAPVC) was first reported by Muller[1] in 1951. Before 1970, the surgical mortality for the correction of this anomaly was significantly higher in infancy. Some authors regarded young age as a major factor in determining mortality.[2] More recently, improved results have been reported in infancy, and young age at operation has not been considered a risk factor.[3–6] These authors generally agreed that any delay in effective surgical treatment of symptomatic infants gives rise to a higher operative mortality. They also noted that mortality was most closely related to the anatomical type of anomalous pulmonary venous return. In a recent study, multivariant analysis showed no significant association between early mortality and age or weight at operation, preoperative pulmonary or systemic pressure and the preoperative condition of patients undergoing surgery.[7]

We retrospectively reviewed 83 patients with isolated TAPVC treated consecutively at our institution between 1973 and 1986. Excluded were patients with atrial isomerism and any who did not have concordant atrioventricular and ventriculoarterial connections. This study seeks to identify the incremental risk factors for death in the total surgical treatment of TAPVC by 1 surgeon.

Patients: There were 46 boys and 37 girls. Thirty-one had supracardiac drainage, most to the left vertical vein, and one had a supracardiac connection directly to the right superior vena cava (group 1). Infradiaphragmatic drainage was present in 16 (group 2). The anomalous connection was to coronary sinus in 27 (group 3) and directly to the right atrium or mixed in the remaining 8 (group 4.)

From the Department of Pediatric Cardiac Surgery, Brompton Hospital, London, England. Manuscript received February 13, 1987; revised manuscript received October 20, 1987, and accepted October 23.

Address for reprints: Christopher Lincoln, FRCS, Brompton Hospital, London SW3, England.

TABLE I Clinical and Catheterization Data (n = 83)

	Group 1	Group 2	Group 3	Group 4
	Supracardiac (n = 32)	Infracardiac (n = 16)	Coronary Sinus (n = 27)	Mixed (n = 8)
Age at operation (days)	80 (1–180)	14 (1–42)	71 (3–240)	90 (2–120)
Weight (kg)	4 (3–13)	3 (1–4)	4 (2–22)	4 (3–7)
BSA (m^2)	0.26 (0.2–0.4)	0.20 (0.1–0.2)	0.25 (0.1–0.4)	0.25 (0.2–0.3)
Days in hospital before operation	2 (0–11)	1 (0–13)	3 (0–22)	5 (0–21)
pH on admission	7.35 (7.0–7.4)	7.30 (7.2–7.5)	7.35 (7.0–7.5)	7.39 (7.3–7.4)
PA systolic (mm Hg)	60 (18–130)	70 (41–100)	45 (24–114)	46 (20–76)
PVR (units m^2)	4.8 (1.0–9.0)	10 (2–20)	3.0 (3–20)	2.7 (1–3)
Qp/Qs	1.9 (0.8–7.4)	1.4 (0.6–1.9)	2.9 (1.8–4.0)	4.0 (1.0–11)
Hospital survival	30 (93%)	11 (68%)	24 (88%)	6 (75%)

All the above indexes are median with range.
BSA = body surface area; PA = pulmonary artery pressure; PVR = pulmonary vascular resistance; Qp/Qs = pulmonary to systemic blood flow.

The analysis was done using distribution-free methods (instead of more widely used normal-based methods), and the variables have been described in the text in terms of median value and range. The minimum value was usually close to the median.

Patient information at the time of hospital admission is listed in Table I.

In contrast to the whole and other groups, patients in group 2 were smaller and tended to be more critically ill at the time of admission. Median age at operation was 14 days (range 1 to 42), median weight 3 kg (range 1 to 4) and median body surface area 0.2 m^2 (range 0.1 to 0.2). The median for the total number of days spent at the referring hospital before admission to our unit was 1 day (range 0 to 13). Median pH on admission was 7.3 (range 7.2 to 7.5).

Cardiac catheterization and cross-sectional echocardiography (special investigation): Fifty-six patients underwent conventional cardiac catheterization and angiography to establish the diagnosis and to clarify the type of anomalous venous return. Twenty-four were diagnosed by cross-sectional echocardiography alone and 3 underwent surgery on the basis only of clinical examination and appearances of the chest radiograph. In those patients undergoing cardiac catheterization, cineangiography usually delineated the type of TAPVC. Measurements were made of the pulmonary artery systolic pressure, the pulmonary vascular resistance and the pulmonary to systemic flow ratio. Pulmonary vascular resistance was calculated using assumed values for oxygen consumption according to the data of Cayler and Rudolph.[8]

Patients in group 2 had a higher pulmonary artery pressure and greater pulmonary vascular resistance. The median for the pulmonary artery systolic pressure was 70 mm Hg (range 41 to 100) and the pulmonary vascular resistance had a median value of 10 units (range 2 to 48 units). The estimation of pulmonary to systemic flow ratio showed a median of 1.4 (range 0.6 to 1.9) (Table I).

Since 1982, 24 of the last 28 consecutive patients were diagnosed by cross-sectional echocardiography alone. There were 11 with supracardiac and 6 with infracardiac drainage. Pulmonary venous connection was directly to the coronary sinus in 9, whereas 2 patients had mixed anomalous drainage. Cardiac catheterization and angiography were undertaken in 4 patients because the attending physician lacked confidence in the echocardiographic diagnosis or the examamination was technically unsatisfactory.

Operative technique: Two methods of perfusion were employed for surgery. The first, used in 15 patients, was conventional cardiopulmonary bypass with moderate hypothermia and continuous perfusion. The second was surface cooling followed by limited perfusion, profound hypothermia and circulatory arrest. In all patients the heart was exposed through a conventional vertical median sternotomy.

Immediate postoperative management: An indwelling pulmonary arterial monitoring line was placed at surgery in all patients with suspected or proven high pulmonary arterial pressure and pulmonary vascular resistance. Pulmonary hypertensive crises were recognized and treated in 10 patients. Seven had supracardiac and 3 coronary sinus forms of TAPVC. These crises were manifest by a sudden major clinical deterioration associated with an increase in pulmonary artery pressure to systemic or suprasystemic levels with concomitant evidence of a decrease in cardiac output not precipitated by hypercapnia or hypoxia.[9] In 8 patients, an initial infusion of tolazoline hydrochloride as a bolus of 1 to 2 mg/kg followed by continuous intravenous infusion at 1 to 2 mg/kg resulted in a major improvement in the clinical status associated with a decrease in pulmonary pressure and a reduction in the ratio of pulmonary artery to systemic artery pressure. Three out of 10 patients treated for this complication eventually died.

Late reoperations: Reoperation was necessary in 7 patients. In group 1, 3 patients required the closure of a residual atrial septal defect and 1 underwent obliteration of a persistent left superior vena cava. Two patients in group 3 required reoperation, in 1 case for correction of a persistent atrial septal defect and in the other for redirection of the inferior vena caval inflow into the right atrium, after it had been inadvertently

TABLE II Age at Operation with Hospital Mortality

Age at Operation	All Pt (n = 83)	Group 1 Supracardiac (n = 32)	Group 2 Infracardiac (n = 16)	Group 3 Coronary Sinus (n = 27)	Group 4 Mixed (n = 8)
1–7 days	10 (1)	2 (0)	5 (1)	3 (0)	
8–14 days	12 (3)	6 (0)	6 (3)		
15–21 days	9 (0)		4 (0)	3 (0)	2 (0)
22–28 days	5 (2)	3 (1)		1 (1)	1 (0)
1–2 months	7 (1)	3 (0)	1 (1)	3 (0)	
2–3 months	10 (2)	3 (0)		6 (1)	1 (1)
3–4 months	12 (2)	6 (0)		4 (1)	2 (1)
4–5 months	5 (0)	2 (0)		1 (0)	2 (0)
5–6 months	6 (0)	4 (0)		2 (0)	
6–>12 months	7 (1)	3 (1)		4 (0)	

TABLE III Total Anomalous Pulmonary Venous Connection (30-Day Hospital Mortality)

	Pt	Deaths (%)	75% CL
Supracardiac	32	2 (6)	2–16
Infradiaphragmatic	16	5 (31)	18–47
Coronary sinus	27	3 (11)	4–21
Mixed	8	2 (25)	8–49
Total	83	12 (14)	10–19

75% CL = 75% confidence limits.

baffled into the left atrium at the original operation. One patient in group 4 required closure of an atrial septal defect. In 4 of the patients with a residual atrial septal defect a right/left transatrial approach was used together with enlargement of the atrial septum.

Statistical methods: Because the samples were independent, the median test, the Wilcoxon Rank Sum test, the Wald-Wolfowitz Runs test and the Komolgorov-Smirnov 2-sample test were used to consider differences. When the data was binary, the chi-square analysis or Fisher's exact tests were used. Results were appraised throughout on a 1-tailed basis. When the total of 83 patients is split into groups the numbers become rather small (e.g., for group 4, n = 8 only) and a statistical result which is not significant but which does show a trend might justify being regarded as not proven.

Results

Of the 83 patients, 12 (14%) died within 30 days of surgery. There were 2 deaths in group 1, 5 in group 2, 3 in group 3 and 2 in group 4 (Table II and III). Causes of death were refractory low cardiac output (4), recurrent pulmonary hypertensive crises (3), supraventricular arrhythmias (1), acute renal failure (1) and cardiac failure (1). Six patients died >30 days after surgery. In 2 of them there was pulmonary venous obstruction at the site of the anastomosis, between the pulmonary venous confluence and the morphological left atrium. Death occurred 2.5 months and 6.5 years after the operation. The cause of death in the remaining 4 was not known.

Actuarial analysis of long-term survival showed that the probability of survival, based on all 83 patients entering the study, was 75% at 84 months. Similar figures were obtained for groups 1, 3 and 4. However, the probability of survival of the 13 patients in group 2 was 60% at 72 months.

Analysis of risk factors: Statistical analysis in regard to survival within the 30-day hospital period was applied to a number of "supposed" risk factors. These were sex of patient, year of operation in the series, age at operation, height and weight (each expressed as percentiles), body surface area, number of days in the hospital prior to operation and systemic arterial pH on admission. Also included were the pulmonary artery systolic pressure and pulmonary vascular resistance in those patients who had undergone cardiac catheterization. We also took into account the method of diagnosis—cardiac catheterization, cross-sectional echocardiography alone and clinical evaluation. Finally, we analyzed the following variables: type of perfusion used, surgical approach, occurrence of pulmonary hypertensive crisis, anatomy of the defect, presence of cyanosis and heart failure, need for preoperative ventilation and presence of preoperative or postoperative renal failure.

The following factors showed a significant difference regarding survival within the 30-day hospital period for the whole group of patients. Risk of hospital death was greater in group 2 ($p < 0.009$). The presence of postoperative pulmonary hypertensive crises had significance ($p < 0.01$), the first 3 years of the study (1973–1975) having a higher risk than the remaining years and with the break at 1975/1976 ($p < 0.02$); it was also shown that females were more at risk than males ($p < 0.05$). Preoperative heart failure ($p < 0.01$) and preoperative renal failure ($p < 0.001$) were additional risk factors influencing survival. The only factor that improved the chance of survival was a diagnosis made on the basis of cross-sectional echocardiography without cardiac catheterization ($p < 0.05$).

Four of the last 28 patients have undergone cardiac catheterization. One of them died in the early postoperative period from obstructed pulmonary venous return.

Discussion

Retrospective statistical analysis of "risk factors" in the whole group of 83 patients shows 7 significant factors influencing successful surgical treatment. There was a higher incidence of death among female patients ($p < 0.05$). The year of operation was important in that there was a striking decrease in mortality from 1976 onwards ($p < 0.02$) reflecting chronological issues, in retrospective analysis of biomedical data.[10] The presence of pulmonary hypertensive crises in the postoperative period was another determinant of outcome because of the high probability of hospital death accompanying them ($p < 0.01$). Heart failure ($p < 0.01$) and preoperative renal failure ($p < 0.001$) similarly influenced survival by increasing the risk of hospital death. Only when the patients were diagnosed by cross-sectional echocardiography alone and were not submitted to conventional cardiac catheterization and angiography was there a significant improvement in survival ($p < 0.05$). Thus, of the 19 factors analyzed, 7 were significant.

Analyses of the 32 patients with supracardiac TAPVC showed that only postoperative pulmonary hypertensive crisis was a significant determinant of unsuccessful treatment ($p < 0.05$). Similarly, in those 27 patients with total anomalous pulmonary venous drainage to coronary sinus there was only 1 statistically significant factor influencing mortality: preoperative heart failure ($p < 0.05$), defined in this study as liver enlargement and a respiratory rate of >40 per minute. Analysis of risk factors in patients with the infracardiac type of anomaly showed a higher mortality in females ($p < 0.02$) and a greater risk of death before 1976 ($p < 0.02$). A raised pulmonary artery systolic pressure ($p < 0.1$) also increased the probability of death. That female patients were apparently disadvantaged may reflect their low weight and body surface area, although this could not be demonstrated statistically.

From 1973 to 1975, the treatment of 13 patients in our series resulted in a hospital mortality of 46%. Since that time, 70 patients have been treated with a mortality of 8.5%, giving a current overall mortality of 14% over a 13-year period. This in part may reflect the "era effect" on the unit and its personnel.[10]

The risk of surgical death is greatly increased in patients with infracardiac anomalous connection. This largely reflects the aforementioned risk factors because the surgical technique to repair the defect is not dissimilar to that for other forms of TAPVC. The recognition of postoperative pulmonary hypertensive crises in 1978 established that these patients are at risk from them and that they can be effectively treated by specific pharmacological agents.[9] The work of Haworth and Newfeld showed that structural changes in pulmonary arterial and venous channels reflecting pulmonary vascular disease may be present in neonates and infants, including TAPVC.[11,12] Newfeld's observation that the degree of pulmonary vascular disease found at autopsy did not correlate well with the pulmonary to systemic systolic blood pressure ratio at cardiac catheterization lends credence to our own observations that patients with preoperative pulmonary artery pressure and pulmonary vascular resistance within normal limits may experience postoperative pulmonary hypertensive crises. The physiological implication of these pulmonary vascular changes is a highly reactive pulmonary vascular bed. We consider it important, therefore, to monitor the pulmonary artery pressure during the early postoperative period.

In the last 28 consecutive patients treated in this series, only 4 were investigated by conventional cardiac catheterization and angiography for the reasons already outlined. The remainder underwent surgery when the diagnosis was established by cross-sectional echocardiography alone. There was 1 mistake in the type of anatomy suggested by this technique but no patient died. In our analysis of risk factors, investigation by cross-sectional echocardiography alone was the only significant factor in improving the chance of survival. Although the surgical treatment of TAPVC solely on the basis of cross-sectional echocardiography has been reported,[13] it was not considered at that time to be significant in improving survival. Our study has shown that by avoiding cardiac catheterization surgical mortality is significantly reduced. It is our current practice, therefore, always to use cross-sectional echocardiography as the final arbiter in the diagnosis of TAPVC.

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Accuracy of Electrical Impedance Cardiography for Measuring Cardiac Output in Children with Congenital Heart Defects

DANIEL S. MILES, PhD, ROBERT W. GOTSHALL, PhD, JANE C. GOLDEN, MS, DWIGHT T. TUURI, MD, ROBERT H. BEEKMAN III, MD, and TERRENCE DILLON, MD

This study determined whether noninvasive electrical impedance cardiography accurately measures systemic blood flow (cardiac output) in children with congenital heart defects. A total of 37 patients ranging in age from 2 to 171 months underwent complete right- and left-sided heart catheterizations that included simultaneous Fick and impedance measurement of cardiac output. Based on the diagnosis, 4 groups were formed consisting of a control group (n = 11) with no shunts, a group with intracardiac left-to-right shunting and an atrial septal defect (n = 7), another with a ventricular septal defect (n = 12) and an extracardiac left-to-right shunting with patent ductus arteriosus group (n = 7). Impedance values for systemic blood flow were compared with systemic and pulmonary blood flow obtained by the direct Fick method with measured oxygen consumption. The difference between impedance and Fick systemic blood flow was ≤5% in each of the 4 groups. The highest correlation between impedance and Fick systemic blood flow was with the atrial septal defect group (r = 0.89) and lowest with the ventricular septal defect and control (r = 0.69) groups. Fick pulmonary blood flow was significantly greater than impedance or Fick systemic flow in all 3 shunt groups. Impedance cardiography accurately measured systemic blood flow in children without shunts or valvular insufficiency. Likewise, systemic blood flow was accurately measured by impedance in the presence of intracardiac left-to-right shunts (atrial and ventricular septal defects) and extracardiac left-to-right shunts (patent ductus arteriosus). Although such results are promising, further studies are needed to evaluate the role of impedance cardiography in pediatric medicine.

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Impedance cardiography is a noninvasive technique used to measure stroke volume on a beat-by-beat basis.[1-4] Most validation studies[1,5,6,7] and clinical trials[8,9] have used adults or animal models almost exclusively. The application of this technique in a neonatal or pediatric population has received very little attention.[10-15] Due to its ease of application, cost effectiveness and atraumatic nature, impedance cardiography may provide an effective adjunct for assessing a child's cardiovascular status or response to medical or surgical therapy.

Our preliminary work with canine pups[6] and neonates[16] suggested that the impedance technique may prove useful in measuring cardiac output in premature newborns, neonates and children. We were particularly interested in evaluating whether the impedance technique could measure cardiac output in children with a congenital heart defect. The only previous study to evaluate children with congenital heart defects reported that the impedance technique overestimated systemic flow but correlated well with pulmonary flow.[14] Unfortunately, because oxygen consumption was estimated in that study,[14] the Fick blood flow measurements may have been questionable. The present study determines whether impedance cardiography accurately measures cardiac output in the presence of

From the Department of Physiology and Biophysics, School of Medicine and College of Science and Mathematics, Wright State University, and the Department of Pediatrics, The Children's Medical Center, Dayton, Ohio. This work was supported by a grant from the Miami Valley Chapter of the American Heart Association, Dayton, Ohio. Manuscript received August 10, 1987; revised manuscript received and accepted November 2, 1987.

Dr. Beekman's present address: C.S. Mott Children's Hospital, University of Michigan, F1123 Box 66, Ann Arbor, Michigan.

Ms. Golden's present address: Physical Therapy Education, 2600 Steindler Building, University of Iowa, Iowa City, Iowa.

Address for reprints: Daniel S. Miles, PhD, Department of Physiology and Biophysics, School of Medicine, Wright State University, Dayton, Ohio 45401-0927.

either intracardiac or extracardiac shunting in children with congenital heart defects.

Methods

Patients: All participants underwent complete right- and left-sided heart catheterizations to confirm the diagnosis, evaluate the extent of a congenital defect or determine the success of corrective surgery. All catheterizations were completed at The Children's Medical Center. Approval for this study was obtained from the Wright State University's Human Subjects Institutional Review Board and the hospital's review board. A total of 37 participants were divided into 4 groups based on the diagnosis. No shunts were present in a control group of patients (n = 11) presenting with a variety of disorders, such as aortic or pulmonary stenosis or aortic coarctation, as well as successfully repaired shunts. Intracardiac shunts were present in the secundum atrial septal defect (ASD) group (n = 7) and in the ventricular septal defect (VSD) group (n = 12). Extracardiac shunts occurred with patent ductus arteriosus (PDA) patients (n = 7). Descriptive characteristics are listed in Table I.

Catheterization: The patients were sedated preoperatively with a variety of medications such as morphine, vistaril, chlorohydrate or ketamine. The right femoral vein was used for right-heart catheterization. The inguinal region was infiltrated with 1 to 2% xylocaine or lidocaine before percutaneous insertion of a Berman or Edwards angiographic catheter (4 to 8Fr) and passed with the aid of fluoroscopy. Left-heart catheterization was performed by inserting a regular Cook pigtail catheter (3 to 6 Fr) into the femoral artery. Pressures were measured with a fluid-filled transducer and recorded on a 4-channel oscillographic recorder (Electronics for Medicine).

Cardiac output: Systemic and pulmonary blood flows were measured by the direct Fick procedure. The direction and magnitude of shunting were also calculated using this procedure, with the superior vena cava providing the mixed venous sample. Oxygen saturation was measured (American Optical Unistat Oximeter) using 0.25 ml aliquots of blood. Blood oxygen carrying capacity was calculated as hemoglobin (g/dl) × 1.36. Oxygen consumption was measured with a Waters instruments continuous flow-through head-box system (MRM2 - O_2 Consumption Monitor). An average of three 1-minute samples was used in the calculations.

TABLE I Descriptive Characteristics (Mean ± Standard Error and Range) of the Patients

Pt	Control (n = 11)	ASD (n = 7)	VSD (n = 12)	PDA (n = 7)
Age (mo)	58 ± 12 (6–130)	72 ± 22 (6–171)	32 ± 9 (2–90)	39 ± 12 (9–88)
Height (cm)	100 ± 7 (63–140)	109 ± 14 (57–164)	86 ± 6 (56–120)	89 ± 7 (68–107)
Weight (kg)	16.7 ± 3 (5–35)	25.7 ± 7 (8–60)	11.8 ± 2 (4–20)	12.7 ± 1.8 (6–20)

ASD = atrial septal defect; control = no shunts; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

Cardiac output was measured by impedance at the time of the oxygen consumption measurements.[17] Mylar tape electrode strips were positioned on the forehead, circumferentially around the neck and on a midaxillary to midaxillary line at the level of the xiphisternal notch and lower abdomen (Figure 1). The Minnesota Impedance Cardiograph Model 304B was used to introduce a constant sinusoidal alternating current of 4 mA at 100 kHz between the outer 2 electrodes (the inner electrodes are sensing electrodes and detect changes in voltage). Knowing the current applied and voltage produced, the cardiograph calculates the impedance based on Ohm's law. Heart sounds were measured at the lower sternal border using a Hewlett Packard microphone (21050 A) and the electrocardiogram was obtained from an Electronics for Medicine ECG amplifier.

The electrical impedance technique provides real-time values of stroke volume which are used with the heart rate to determine cardiac output.[2,4] The stroke volume is derived from analysis of the change in impedance with respect to time (dZ/dt) during the cardiac cycle. The electrocardiogram, phonocardiogram and dZ/dt were recorded at a paper speed of 100 mm/s with a Gould 4-channel strip-chart recorder (Figure 1). The equation used to calculate stroke volume was $SV = p \cdot (L/Z_0)^2 \cdot dZ/dt \cdot T$ and expressed as follows: $SV = (\Omega \cdot cm)(cm^2/\Omega^2)(\Omega/s)(s) = cm^3$ (ml), where SV = stroke

TABLE II Summary (Mean ± Standard Error and Range) of the Catheterization Procedure

	HR	$\dot{V}O_2$	$\dot{Q}PI/\dot{Q}SI$	LRS	RLS	RP/RS
Control	102 ± 5.3 (81–146)	156 ± 8.1 (130–212)	1.0	0	0	0.13 ± 0.02 (0.06–0.30)
ASD	100 ± 6.6 (75–128)	119 ± 7.0 (98–147)	2.60 ± 0.36 (1.3–4.5)	4.68 ± 0.66 (1.4–7.0)	0.02 ± 0.02 (0–0.1)	0.04 ± 0.008 (0.02–0.07)
VSD	122 ± 6.8 (86–152)	165 ± 9.4 (125–225)	2.30 ± 0.38 (1.3–6.0)	5.55 ± 1.21 (1.2–16.7)	0	0.09 ± 0.02 (0.04–0.21)
PDA	102 ± 6.9 (79–135)	151 ± 8.8 (125–196)	1.86 ± 0.15 (1.3–2.3)	3.84 ± 0.59 (1.4–6.0)	0	0.09 ± 0.03 (0.05–0.26)

HR = heart rate (beats/min); LRS = left-to-right shunt (liters/min/m^2); $\dot{Q}PI/\dot{Q}SI$ = ratio of pulmonary to systemic cardiac index; RLS = right-to-left shunt (liters/min/m^2); RP/RS = ratio of pulmonary to systemic resistance; $\dot{V}O_2$ = oxygen consumption (cc/min/m^2). Other abbreviations as in Table I.

TABLE III Summary (Mean ± Standard Error and Range) of Direct Fick and Impedance Blood Flow

	$\dot{Q}S$	$\dot{Q}Z$	$\dot{Q}P$
Control	3.09 ± 0.45 (0.96–5.17)	3.22 ± 0.59 (0.41–6.31)	3.09 ± 0.45 (0.96–5.17)
ASD	2.72 ± 0.49 (0.36–4.10)	2.86 ± 0.71 (0.41–5.62)	6.56* ± 1.30 (1.63–10.96)
VSD	2.59 ± 0.36 (0.87–4.51)	2.52 ± 0.48 (0.26–5.95)	5.02* ± 0.47 (1.97–7.33)
PDA	2.48 ± 0.35 (1.34–3.75)	2.49 ± 0.44 (0.90–3.76)	4.51* ± 0.62 (2.46–6.51)

* $p < 0.05$, $\dot{Q}P > \dot{Q}S$ or $\dot{Q}Z$.

$\dot{Q}P$ = Fick pulmonary blood flow (liters/min); $\dot{Q}S$ = Fick systemic blood flow (liters/min); $\dot{Q}Z$ = impedance systemic blood flow (liters/min). Other abbreviations as in Table I.

volume (ml); p = resistivity (Ω · cm) of blood and assumed to be a constant[18] of 135; L = anterior midline distance between the inner electrodes (cm); Z_0 = total thoracic impedance (Ω) between the sensing electrodes (2 and 3); dZ/dt = the maximum rate of change of the thoracic impedance (Ω/s) during each heart beat measured from the beginning of the rapid upstroke independent of the calibration baseline as previously described in our laboratory[19]; T = left ventricular ejection time (s).

Heart rate was determined on a beat-by-beat basis from the Q-Q interval of the electrocardiogram and multiplied by stroke volume to obtain impedance systemic blood flow. The mean impedance blood flow was obtained by averaging 10 heartbeats. Impedance data were hand-digitized on a Houston Instruments True Grid 1017 digitizing pad interfaced with an IBM-PC XT computer.

Statistical analyses: Means, standard errors, regression analysis, correlations and Student-dependent *t* test were run using the Crunch Interactive Statistical Package (CRISP). All null hypotheses were rejected at the 5% level.

Results

Heart rates for the 4 groups were similar during catheterization (Table II). The greater Fick pulmonary blood flow in the ASD, VSD and PDA groups (compared with Fick systemic blood flow) could be attributed to the left-to-right shunting. The ratio of pulmonary resistance to systemic resistance was similar in all groups.

The systemic blood flow measured by impedance was similar ($r = 0.84$, $p < 0.05$) to Fick measurements (Table III, Figure 2). The difference between the blood flow values for the 2 techniques was ≤5% in each of the 4 groups (Figure 3). Blood flow correlations between the 2 techniques ranged from 0.69 to 0.89, with the highest in the ASD group and lowest in the VSD

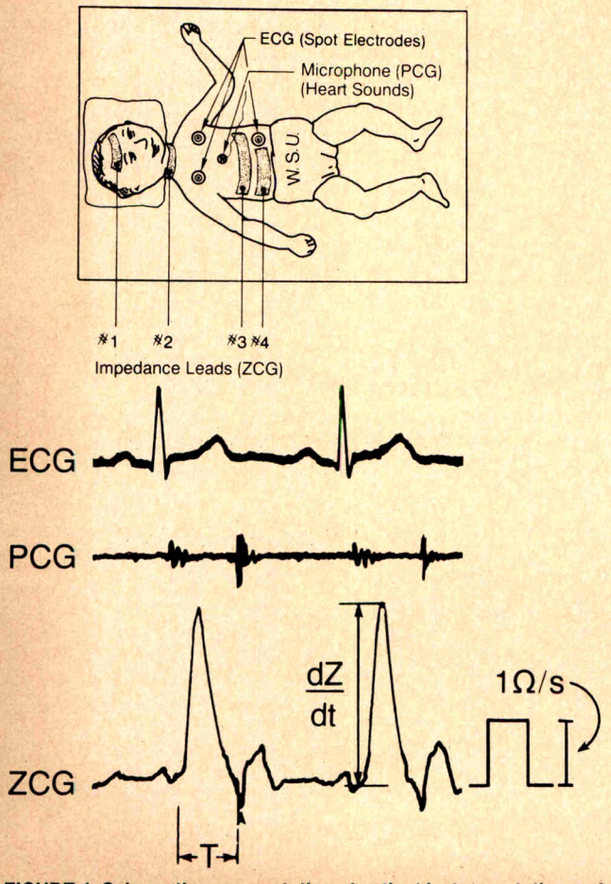

FIGURE 1. Schematic representation of patient instrumentation and records of the electrocardiogram (ECG), phonocardiogram (PCG) and impedance cardiogram (ZCG).

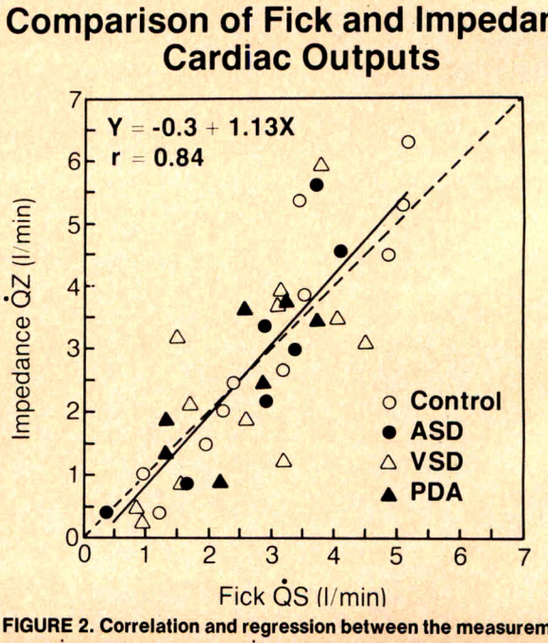

FIGURE 2. Correlation and regression between the measurement of Fick ($\dot{Q}S$) and impedance ($\dot{Q}Z$) systemic blood flow for all subjects including atrial septal defects (ASD), ventricular septal defects (VSD), patent ductus arteriosus (PDA) and no shunts (control).

and control groups. Fick pulmonary blood flow was significantly greater than systemic flow as determined by either Fick or impedance in the ASD, VSD and PDA groups (Table III, Figure 3).

Discussion

Repeated tests can be easily administered using the impedance technique for assessment of cardiac output without any known risk or discomfort to the patient. It may prove to be particularly useful in providing a means to serially evaluate patients after surgery or over the course of medical or surgical management. It must be convincingly demonstrated, however, that an accurate estimate of cardiac output is being measured. The present patient population offered an opportunity to evaluate the impedance technique using the established direct Fick procedure as the standard. Nevertheless, it should be noted that even blood flow measured by the direct Fick procedure is not without inherent errors.

Very few studies evaluating neonates or children with impedance cardiography have been published. We have previously reported that healthy premature infants weighing 0.8 to 3.8 kg could be evaluated accurately.[16] Premature infants with patent ductus arteriosus,[20,21] healthy newborn infants[11,12,22] and children[23] also have been studied. In general, these studies have reported cardiac output values consistent with the population under consideration but lacked a comparison with an invasive technique. The work of Lababidi et al[14] is the only other study published where a comparison between direct Fick values of cardiac output and impedance has been evaluated in children with and without cardiac shunts.

Our results were similar to Lababidi et al in demonstrating that cardiac outputs measured by either the Fick or impedance techniques were similar (r = 0.69) in children without shunts or valvular insufficiency. Our results were at variance, however, with their values reported for children with intracardiac left-to-right shunting. When they evaluated 21 patients with left-to-right shunts, the impedance cardiac output overestimated systemic flow and correlated well with pulmonary blood flow (r = 0.92) rather than systemic flow (r = 0.21). In sharp contrast, our findings suggested close agreement between the Fick and impedance systemic blood flow measurements in either the ASD (r = 0.89) or VSD (r = 0.69) groups.

The reason for the discrepancy between the 2 studies of patients with intracardiac shunts is not readily apparent. Oxygen consumption was directly measured in the present study whereas in the Labibidi et al study it was estimated. It has been demonstrated that oxygen consumption in sedated children varies during catherization procedures[24] and that oxygen consumption is higher in children with cardiovascular disease.[25] If oxygen consumption was underestimated by Lababidi et al, Fick estimates of pulmonary and systemic flow would also be underestimated. Perhaps this may explain some of the observed differences. Furthermore, we used a constant of 135 Ω · cm for the blood resistivity factor in our calculation of stroke volume,[18] whereas Lababidi et al based blood resistivity calculations on the hematocrit. The total number of patients evaluated with intracardiac shunts was only 19 in the present study and 21 in Lababidi's. Clearly, further data are needed before a definitive conclusion can be drawn.

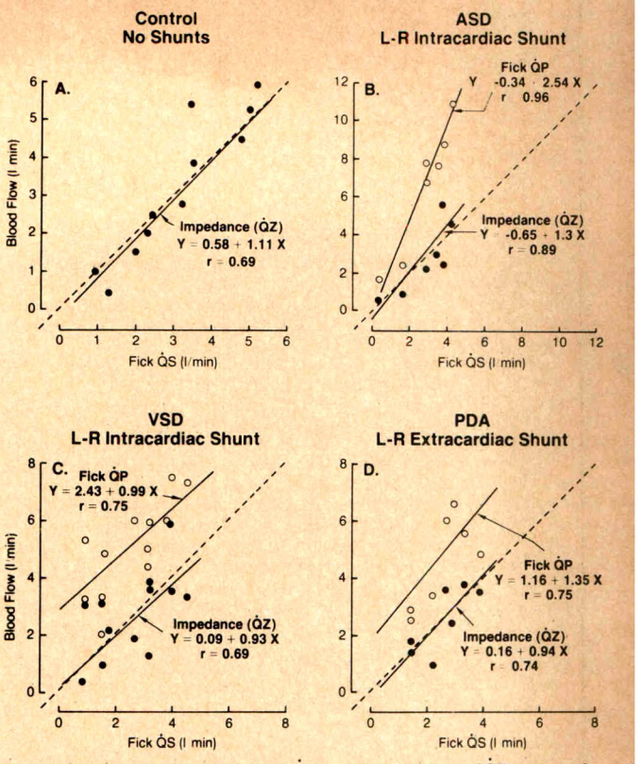

FIGURE 3. Individual systemic (Q̇S) and pulmonary (Q̇P, open circles) blood flow determined by the Fick procedure, and systemic blood flow determined by impedance (Q̇Z) for (*A*) control, (*B*) atrial septal defect (ASD), (*C*) ventricular septal defect (VSD) and (*D*) patent ductus arteriosus (PDA) groups.

In the patients with PDA (extracardiac left-to-right shunts), impedance measurements reflected systemic blood flow (r = 0.74). Pulmonary blood flow measured by the Fick technique was consistently higher than either Fick or impedance systemic flow in all patients. These results were again at variance with the only 2 previously published studies of patent ductus arteriosus patients.[20,21] Cotton et al[20] reported that the magnitude of the ΔZ signal using a tetrapolar electrode configuration was indicative of pulmonary blood flow in infants with symptomatic PDA. Spontaneous or pharmacologic closure of the ductus was coincident with an amplitude decrease in the ΔZ signal. Cardiac output, however, was not measured. Sexson et al[21] demonstrated in a preliminary report that indomethacin significantly reduced cardiac output within 24 hours of therapy for treatment of PDA. Neither the study by Cotton et al[20] nor Sexson et al[21] used an alternative technique for corroboration of the impedance values.

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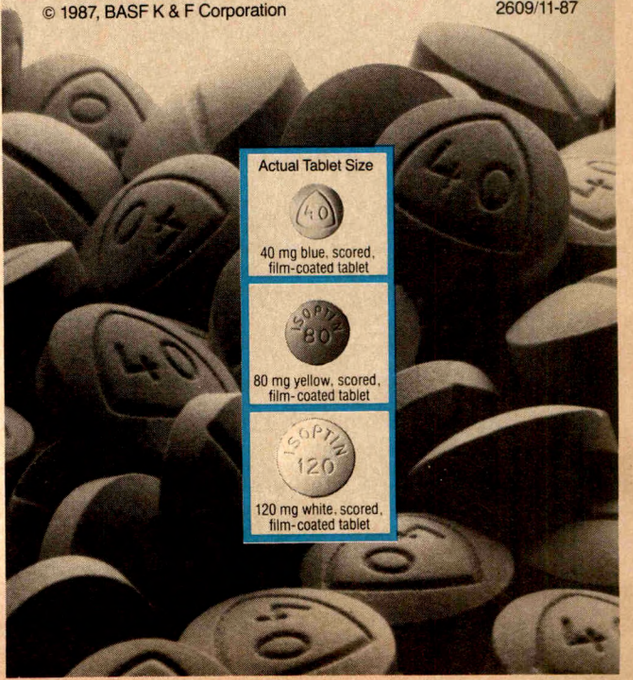

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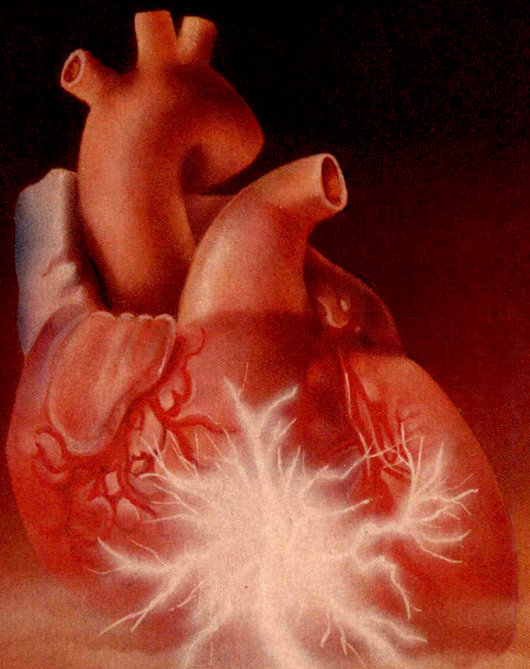

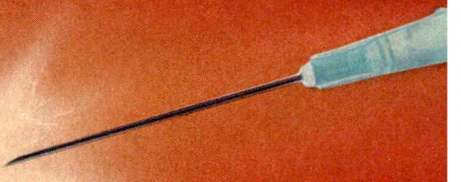

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in Acute MI

Geigy

Lifesaving

- 36% reduction in 3-month mortality[1]
- Reduced incidence of arrhythmias and ischemic pain[1]

Safe

- >93% tolerated the full intravenous dose[2]
- <1% withdrawn for congestive heart failure[3]

Intravenous followed by long-term oral therapy

Alternatively, oral treatment can begin within 3 to 10 days of the acute event

Lopressor is contraindicated in patients with heart rate <45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥0.24 sec); systolic blood pressure <100 mmHg; or moderate-to-severe cardiac failure.

Please see last page for Brief Summary of Prescribing Information.

The *only* beta blocker indicated in definite or suspected acute myocardial infarction...

Lopressor® in MI

metoprolol tartrate

Prefilled Syringes: 5 mg/5 ml
Ampuls: 5 mg/5 ml
Tablets: 100 mg 50 mg

Changing the Course of Cardiovascular Care

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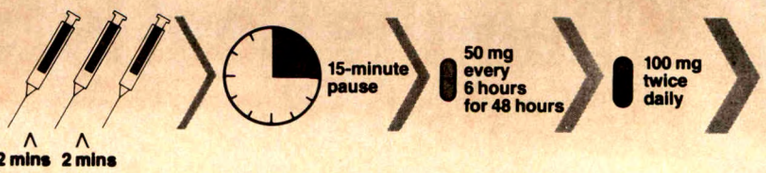

Lopressor®

metoprolol tartrate USP

Tablets
Ampuls
Prefilled Syringes

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

Hypertension
Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris
Lopressor is indicated in the long-term treatment of angina pectoris.

Myocardial Infarction
Lopressor ampuls, prefilled syringes, and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS

Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS

General
Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypertension and Angina
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.

Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

C86-36 (Rev. 6/86)

Geigy

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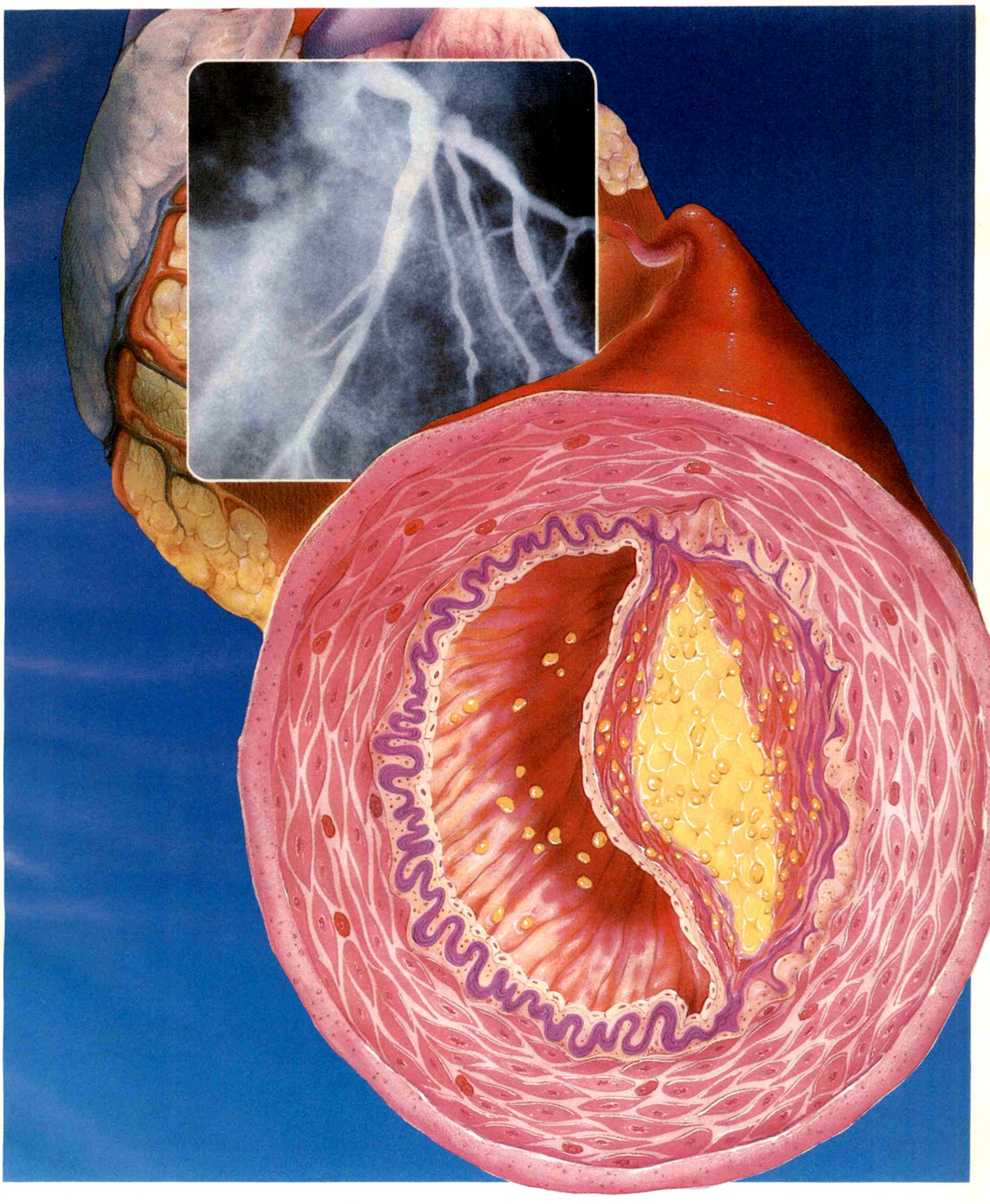
When the Goal Is to Reduce Elevated Blood Cholesterol...



LORELCO®
PROBUCOL 250 mg tablets

Prescribing Information appears on the last page.

Choose

LORELCO® PROBUCOL

250 mg tablets

as an adjunct to diet

Effectively Lowers Serum Cholesterol with a Unique Combination of Benefits

1 Efficacy

Lorelco works! You can prescribe it with confidence. Lorelco can virtually double the cholesterol-lowering efficacy of diet alone.[1] Total cholesterol-lowering efficacy *beyond diet* ranges from 10.7% to 27% in reported studies.[1-4]

2 Indications

Lorelco is specifically indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia who have not responded adequately to diet.

Consider the Whole Picture.

Merrell Dow

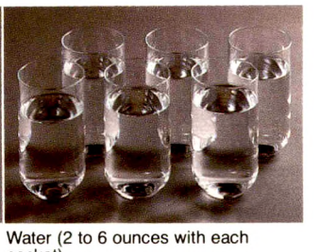
#1 selling lipid-lowering agent in the world

3 Compliance

The reasons for excellent compliance with Lorelco become clear with the taste and texture test.

This

Questran daily dose (one 9-gram packet one to six times daily)



Water (2 to 6 ounces with each packet)

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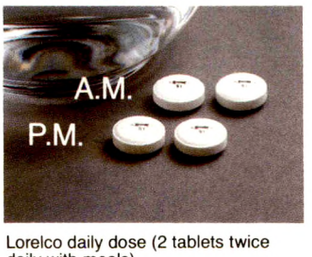

Lorelco daily dose (2 tablets twice daily with meals)

Tablet counts in a 7 year study of Lorelco indicated that patients took over 90% of their scheduled dosage.[5]

4 Side Effects

Lorelco side effects are generally tolerable and of short duration.

Most frequent patient complaint is loose stools, which occur in about one in 10 patients and generally subside during therapy (see Prescribing Information for full discussion of side effects).

Lorelco is not an innocuous drug and strict attention should be paid to the Indications, Warnings, and Precautions.

5 Cost

The cost of Lorelco is significantly lower than that of the resins, lovastatin, and niacin tablets USV.

Cost can be a significant factor when therapy may have to be continued long-term, perhaps for years.

10 years of outstanding Lorelco performance[6]

Now prescribed in 27 countries

The effect of probucol-induced reduction of serum cholesterol or triglyceride levels or alteration of HDL-cholesterol levels on morbidity or mortality has not yet been established. Several years may be required before ongoing long-term investigations will resolve this question.

Prescribing Information appears on the last page.

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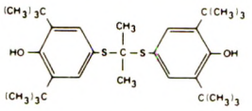
6. Data on file, MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242.

Lorelco® Tablets
(probucol tablets)

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION: Lorelco (probucol) film-coated tablets for oral administration contain 250 mg of probucol per tablet. Each tablet also contains as inactive ingredients: corn starch, ethylcellulose, glycerin, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2910, iron oxide, lactose, magnesium stearate, microcrystalline cellulose, polysorbate 80, talc, and titanium dioxide. Lorelco is an agent for the reduction of elevated serum cholesterol. The chemical name is 4,4'-(isopropylidenedithio) bis (2,6-di-t-butylphenol). Its chemical structure does not resemble that of any other available cholesterol-lowering agent. It is lipophilic.



CLINICAL PHARMACOLOGY: Lorelco (probucol) lowers serum cholesterol and has relatively little effect on serum triglycerides. Patients responding to probucol exhibit a decrease in low density lipoprotein cholesterol. Cholesterol is reduced not only in the low density lipoprotein fraction, but also in some high density lipoprotein fractions with proportionately greater effect on the high density portion in some patients. Epidemiological studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease. The risk of lowering HDL-cholesterol while lowering LDL-cholesterol remains unknown. There is little or no effect reported on very low density lipoprotein.

Studies on the mode of action of Lorelco indicate that it increases the fractional rate of catabolism of low density lipoproteins. This effect may be linked to the observed increased excretion of fecal bile acids, a final metabolic pathway for the elimination of cholesterol from the body. Lorelco also exhibits inhibition of early stages of cholesterol synthesis and slight inhibition of absorption of dietary cholesterol. There is no increase in the cyclic precursors of cholesterol, namely desmosterol and 7-dehydrocholesterol. On this basis, it is concluded that Lorelco does not affect the later stages of cholesterol biosynthesis.

Absorption of Lorelco from the gastrointestinal tract is limited and variable. When it is administered with food, peak blood levels are higher and less variable. With continuous administration in a dosage of 500 mg b.i.d., the blood levels of an individual gradually increase over the first three to four months and thereafter remain fairly constant. In 116 patients treated with Lorelco for periods of three months to one year, the mean blood level was 23.6 ± 17.2 mcg/ml (± S.D.) ranging to 78.3 mcg/ml. Levels observed after seven years of treatment in 40 patients yielded an average value of 21.5 ± 16.5 mcg/ml (± S.D.) ranging to 62.0 mcg/ml.

At the end of 12 months of treatment in eight patients, blood levels averaged 19.0 mcg/ml. Six weeks after cessation of therapy, the average had fallen by 60 percent. After six months the average had fallen by 80 percent.

In December 1984 a National Institutes of Health Consensus Development Conference Panel† concluded that lowering definitely elevated blood cholesterol levels (specifically blood levels of low-density lipoprotein cholesterol) will reduce the risk of heart attacks due to coronary heart disease. The effect of probucol-induced reduction of serum cholesterol or triglyceride levels or alteration of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not yet been established. Several years may be required before ongoing long-term investigations will resolve this question.

INDICATIONS AND USAGE: Serious animal toxicity has been encountered with probucol. See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections. Probucol is not an innocuous drug and strict attention should be paid to the INDICATIONS and WARNINGS.

Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight may be an important factor and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory disease such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision ultimately is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

The selection of patients for cholesterol-lowering drug therapy should take into account other important coronary risk factors such as smoking, hypertension and diabetes mellitus. Consideration should be given to the efficacy, safety and compliance factors for each of the cholesterol-lowering drugs prior to selecting the one most appropriate for an individual patient.

Lorelco may be indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoproteins) who have not responded adequately to diet, weight reduction and control of diabetes mellitus. Lorelco may be useful to lower elevated cholesterol that occurs in patients with combined hypercholesterolemia and hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.

It is not always possible to predict from the lipoprotein type or other factors which patients will exhibit favorable results. Lipid levels should be periodically assessed. Small or transient changes in high density lipoprotein cholesterol may be due to inaccuracies in the method of determination. Substantial changes are sometimes seen with diet.

The effect of probucol-induced reduction of serum cholesterol or triglyceride levels or alteration of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not yet been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS: (See also PRECAUTIONS.) Lorelco is contraindicated in patients who are known to have a hypersensitivity to it.

WARNINGS: SERIOUS ANIMAL TOXICITY HAS BEEN ENCOUNTERED WITH PROBUCOL IN RHESUS MONKEYS FED AN ATHEROGENIC DIET AND IN BEAGLE DOGS. (SEE ANIMAL PHARMACOLOGY AND TOXICOLOGY SECTION.)

Although Q-T prolongation can occur in patients on probucol, the arrhythmias observed in monkeys fed large doses of probucol added to an atherogenic diet have not been reported in man; nevertheless, the following precautions are deemed prudent:

1. At the start of treatment with Lorelco and throughout the treatment period, patients should be advised to adhere to a low cholesterol, low fat diet.
2. As part of an overall evaluation, a baseline, six month, and one year repeat ECG tracing should be considered. If marked prolongation of the Q-T interval (after correction for rate) occurs, the possible benefits and risks should be carefully considered before making the decision to continue the probucol administration.

Lorelco should not be used in patients with evidence of recent or progressive myocardial damage or findings suggestive of ventricular arrhythmias.

No instances of increase in ectopy attributed to Lorelco have been reported. However, patients with unexplained syncope while on Lorelco should have ECG surveillance.

PRECAUTIONS

General: Because Lorelco is intended for long-term administration, adequate baseline studies should be performed to determine that the patient has elevated serum cholesterol levels. Serum lipid levels should be determined before treatment and repeated during the first few months of treatment and periodically thereafter. A favorable trend in cholesterol reduction should be evident during the first three to four months of administration of Lorelco. Probucol lowers serum total and LDL cholesterol, and also lowers HDL-cholesterol in many patients with elevated LDL-cholesterol. Epidemiologic studies within hypercholesterolemic populations have shown that serum HDL-cholesterol is an independent, inversely correlated, risk factor for coronary heart disease (see CLINICAL PHARMACOLOGY). Animal or human studies which could confirm or deny the hypothesis that drug induced alteration in HDL-cholesterol affects cardiovascular risk have not been carried out. It is not known whether probucol-induced reduction of serum HDL-cholesterol will affect cardiovascular risk since no long-term, controlled clinical trials of probucol for the prevention of coronary heart disease, similar to the LRC-CPPT (See CLINICAL STUDIES), have been performed. The probable benefits obtained from LDL-cholesterol reduction must be weighed against the possible risk of a reduction in HDL-cholesterol when assessing the response of each patient receiving Lorelco treatment. If satisfactory lipid alteration is not achieved, the drug should be discontinued.

Information for Patients: The patient should be instructed to adhere to a prudent diet. Females should be cautioned against becoming pregnant for at least six months after discontinuing Lorelco and should not breast feed their infants during therapy with Lorelco.

Laboratory Tests: The physician should schedule periodic blood lipid determinations and should consider periodic electrocardiograms. (See WARNINGS.)

Elevations of the serum transaminases (glutamic-oxalacetic and glutamic-pyruvic), bilirubin, alkaline phosphatase, creatine phosphokinase, uric acid, blood urea nitrogen and blood glucose above the normal range were observed on one or more occasions in various patients treated with Lorelco. Most often these were transient and/or could have been related to the patient's clinical state or other modes of therapy. Although the basis for the relationship between probucol and these abnormalities is not firm, the possibility that some of these are drug-related cannot be excluded. In the controlled trials, the incidence of abnormal laboratory values was no higher in the patients treated with probucol than in the patients who received placebo. If abnormal laboratory tests persist or worsen, if clinical signs consistent with the abnormal laboratory tests develop, or if systemic manifestations occur, probucol should be discontinued.

Drug Interactions: The addition of clofibrate to probucol is not recommended since the lowering effect on mean serum levels of either LDL or total cholesterol is generally not significantly additive and, in some patients, there may be a pronounced lowering of HDL-cholesterol. Neither oral hypoglycemic agents nor oral anticoagulants alter the effect of Lorelco on serum cholesterol. The dosage of these agents is not usually modified when given with Lorelco. Monkeys fed a high fat, high cholesterol diet admixed with probucol exhibited serious toxicity. The toxicity observed in monkeys has not been reported in man. (See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections.)

Carcinogenesis, Mutagenesis, Impairment of Fertility
In chronic studies of two years duration in rats, no toxicity or carcinogenicity was observed. These results are consistent with the lack of any adverse effect on fertility and the negative findings in tests for mutagenic activity in rats.

Pregnancy
Teratogenic Effects
Pregnancy—Category B: Reproduction studies have been performed in rats and rabbits at doses up to 50 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus due to probucol. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Furthermore, if a patient wishes to become pregnant, it is recommended that the drug be withdrawn and birth control procedures be used for at least six months because of persistence of the drug in the body for prolonged periods. (See CLINICAL PHARMACOLOGY.)

Labor and Delivery: The effect of Lorelco on human labor and delivery is unknown.

Nursing Mothers: It is not known whether this drug is secreted in human milk, but it is likely to be since such excretion has been shown in animals. It is recommended that nursing not be undertaken while a patient is on Lorelco.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Gastrointestinal
diarrhea or loose stools, flatulence, abdominal pain, nausea, vomiting, indigestion, gastrointestinal bleeding

Cardiovascular
prolongation of the Q-T interval on ECG

Neurologic
headache, dizziness, paresthesias, insomnia, tinnitus, peripheral neuritis

Hematologic
eosinophilia, low hemoglobin and/or hematocrit, thrombocytopenia

Dermatologic
rash, pruritus, ecchymosis, petechiae, hyperhidrosis, fetid sweat

Genitourinary
impotency, nocturia

Ophthalmic
conjunctivitis, tearing, blurred vision

Endocrine
enlargement of multinodular goiter

Idiosyncrasies
An idiosyncratic reaction observed with initiation of therapy and characterized by dizziness, palpitations, syncope, nausea, vomiting and chest pain has been observed.

Other
diminished sense of taste and smell, anorexia, angioneurotic edema

DRUG ABUSE AND DEPENDENCE: No evidence of abuse potential has been associated with Lorelco, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE: There is a single report of a 15 kg, three-year-old male child who ingested 5 gm of probucol. Emesis was induced by ipecac. The child remained well, apart from a brief episode of loose stools and flatulence. No specific information is available on the treatment of overdosage with Lorelco and no specific antidote is available. Probucol is not dialyzable. Treatment is symptomatic and supportive. Probucol has shown no identifiable acute toxicity in mice and rats. In these animals the LD_{50} (oral) is in excess of 5 gm/kg of body weight.

DOSAGE AND ADMINISTRATION: For adult use only. The recommended and maximal dose is 500 mg (two tablets of 250 mg each) twice daily with the morning and evening meals.

HOW SUPPLIED: Each white film-coated tablet contains 250 mg probucol and is imprinted with the DOW diamond trademark over the code number 51, or LORELCO 250.
Bottles of 120 tablets, a 30-day supply for one patient (NDC 0068-0051-52)

Keep well closed. Store in a dry place. Avoid excessive heat. Dispense in well closed light-resistant container with child-resistant closure.

ANIMAL PHARMACOLOGY AND TOXICOLOGY: In rhesus monkeys administration of probucol in diets containing unusually high amounts of cholesterol and saturated fat resulted in the death of four of eight animals after several weeks. Premonitory syncope was frequently observed and was associated with a pronounced prolongation of the Q-T intervals (30 to 50 percent longer than that observed in untreated monkeys). Serum levels of probucol greater than 20 mcg/ml were generally associated with some prolongation in the Q-T interval in the cholesterol-fed monkey. A 75 msec or greater increase in Q-T interval from control values was usually seen at 40 mcg/ml and above. Blood levels in humans receiving probucol average approximately 20 mcg/ml and not uncommonly reach levels of 40 mcg/ml and higher. Rhesus monkeys fed normal (low fat) chow and receiving probucol three to thirty times the human dose equivalent achieved blood levels only one-third those of many human subjects. No adverse effects were detected in these monkeys over an eight-year period of continuous drug administration. In another study in rhesus monkeys, an atherogenic diet was fed for two years and daily treatment with probucol, separated in time from the atherogenic meal, was carried out during the second year. Serum probucol levels ranged 20 to 50 mcg/ml in five of ten monkeys, and less in the remaining animals. Marked prolongation of the $Q\text{-}T_c$ interval in the electrocardiogram or syncopal behavior was never observed over the entire one-year treatment period. Regression of gross aortic lesions comparable to that observed in a parallel group of monkeys receiving cholestyramine was seen in animals receiving probucol. It should be emphasized that both HDL-cholesterol and LDL-cholesterol were markedly reduced in this regression study. During the performance of a two-year chronic study involving 32 probucol-treated dogs (beagles) there were 12 fatalities. Subsequent experiments have indicated that probucol sensitizes the canine myocardium to epinephrine, resulting in ventricular fibrillation in many dogs. Among the animal species in which probucol has been studied, the dog is peculiar with respect to the phenomenon of sudden death due to the sensitization of the myocardium to epinephrine. In contrast to findings in the dog, injections of epinephrine to probucol-treated monkeys did not induce ventricular fibrillation.

In other studies, monkeys were given probucol either before and after, or only after myocardial infarction induced by coronary artery ligation. In these studies there was no difference between probucol- and placebo-treated groups with respect to either survival or detailed blind quantitation of myocardial changes (gross and histopathologic).

Probucol has shown no identifiable toxicity in mice and rats. In these animals the LD_{50} (oral) is in excess of five gm/kg of body weight. In chronic studies of two-year duration in rats, no toxicity or carcinogenicity was observed.

From studies in rats, dogs and monkeys, it is known that probucol accumulates slowly in adipose tissue. Approximately 90 percent of probucol administered orally is unabsorbed. For that which is absorbed, the biliary tract is the major pathway for clearance from the body and very little is excreted by way of the kidneys.

Myocardial injury was produced in various groups of rats by one of the following procedures: aortic coarctation, coronary ligation, or cobalt or isoproterenol injection. After probucol administration, no deleterious effects related to treatment occurred as measured by survival and microscopic examination of myocardial damage.

Probucol was administered to minipigs beginning ten days before ligation of coronary artery and continued for 60 days post surgery. Challenge with epinephrine at the end of 60 days failed to induce ventricular fibrillation in any of the coronary-ligated, probucol-treated minipigs.

CLINICAL STUDIES: In a multicenter, randomized, double-blind study, the LRC-CPPT[2], hypercholesterolemic patients treated with an oral bile acid sequestrant (cholestyramine) and a cholesterol lowering diet experienced average total and low-density lipoprotein cholesterol reductions greater than those obtained in the placebo group treated with diet alone. The cumulative seven-year incidence of the primary end point—combined incidence of definite CHD death and/or definite nonfatal myocardial infarction—was 7% in the cholestyramine group and 8.6% in the placebo group. This was a 19% reduction in risk (P less than 0.05, single-tail test) of the primary end point reflecting a 24% reduction in definite CHD death and a 19% reduction in nonfatal myocardial infarction.

The subjects included in the study were middle-aged men (35-59 years old) with serum cholesterol levels at least 265 mg/dl and no previous history of heart disease. It is not clear to what extent these findings can be extrapolated to other segments of the hypercholesterolemic population not studied.

The bile acid sequestrant, cholestyramine was used in the above trial. Caution should be exercised in extrapolating these results to probucol since it differs from cholestyramine with regard to its mode of action, spectrum of cholesterol-lowering potency, effect on HDL-cholesterol and possible toxicity. The effect of probucol-induced reduction of serum cholesterol levels on morbidity or mortality due to coronary heart disease has not yet been established. Several years may be required before ongoing long-term investigations will resolve this question.

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Product Information as of April, 1986 Y196D

MERRELL DOW PHARMACEUTICALS INC.
Subsidiary of The Dow Chemical Company
Cincinnati, Ohio 45215, U.S.A.

Merrell Dow

Effect of Increasing Heart Rate on Left Ventricular Performance in Patients with Normal Cardiac Function

SAUL SCHAEFER, MD, ANNE L. TAYLOR, MD, HOWARD R. LEE, MD, ELAINE H. NIGGEMANN, MD, BENJAMIN D. LEVINE, MD, JEFFREY J. POPMA, MD, JERE H. MITCHELL, MD, and L. DAVID HILLIS, MD

The influence of an increase in heart rate on left ventricular (LV) contractile performance was assessed in patients with normal LV function. In 19 patients (3 men, 16 women) ages 55 ± 9 years (mean ± standard deviation) with normal global and segmental LV function and normal coronary arteries, LV dP/dt max was measured at baseline heart rate and during atrial pacing at baseline +5, baseline +25 and baseline +45 beats/min. In 10 of the patients, intravascular volume was not altered during pacing and, as a result, echocardiographically measured LV end-diastolic dimension decreased (5.4 ± 0.4 at baseline vs 4.9 ± 0.5 cm at baseline +45 beats/min, p <0.05). In these patients, LV dP/dt max increased modestly (1,571 ± 237 at baseline vs 1,760 ± 199 mm Hg/s at baseline +45 beats/min, p <0.05). In the other 9 patients, intravascular volume was expanded rapidly (by saline infusion) during pacing and, as a result, LV end-diastolic dimension was held constant (5.2 ± 0.6 at baseline vs 5.1 ± 0.6 cm at baseline +45 beats/min, difference not significant). In these patients, LV dP/dt max increased substantially with pacing (1,505 ± 228 at baseline vs 2,050 ± 258 mm Hg/s at baseline +45 beats/min, p <0.05). Thus, an increase in heart rate induces a modest increase in LV dP/dt max in patients in whom LV preload (as reflected by end-diastolic dimension) is allowed to decrease; in contrast, it causes a marked increase in LV dP/dt max in those in whom LV preload is maintained constant.

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The strength of contraction of cardiac muscle is augmented when the rate of stimulation is increased.[1] This is true in isolated papillary muscle,[2,3] segments of ventricular myocardium,[4–6] isovolumically contracting ventricle[7–10] and the pumping heart of the anesthetized dog.[11,12] In the conscious dog, a pacing-induced increase in heart rate has been shown to cause a slight decrease[13] or a modest increase[14] in the maximal rate of left ventricular (LV) pressure rise (dP/dt max), a measure of ventricular contractility. During atrial pacing, LV end-diastolic volume declines; as a result, the positive inotropic effect of an increase in heart rate may be offset by a decrease in LV diastolic filling (preload). In fact, when LV preload is held constant during pacing (by the rapid infusion of saline), LV dP/dt max increases modestly (by an average of 14%) instead of decreasing (by an average of 6%).[13]

Previous studies in patients with coronary artery disease[15] or atrial septal defect[16] have yielded similar results, demonstrating that an increase in heart rate (caused by atrial pacing or atropine) induces only a modest increase in LV dP/dt max. As in the aforementioned canine studies, the improvement in LV performance caused by an increase in heart rate may be offset by a decrease in LV diastolic filling. No previously published study has examined the influence of an increase in heart rate on LV performance in patients with normal cardiac function or the magnitude of a pacing-induced increase in LV dP/dt max when

From the Department of Internal Medicine (Cardiovascular Division), the University of Texas Health Science Center, Dallas, Texas. Dr. Hillis is an established Investigator of the American Heart Association, Dallas, Texas. Manuscript received September 1, 1987; revised manuscript received and accepted October 26, 1987.

Address for reprints: L. David Hillis, MD, Room L5.134, University of Texas Health Science Center, 5323 Harry Hines Boulevard, Dallas, Texas 75235.

TABLE I Hemodynamic Responses to Atrial Pacing

	Baseline	Baseline +5 bpm	Baseline +25 bpm	Baseline +45 bpm
Group A (no saline infusion)				
HR (bpm)	77 ± 14*	82 ± 14*	102 ± 14*	122 ± 14*
LVEDD (cm)	5.4 ± 0.4*	5.3 ± 0.5*	5.0 ± 0.4*	4.9 ± 0.5*
SAP (mm Hg)	137 ± 33	140 ± 34	135 ± 33	135 ± 33
LV dP/dt max (mm Hg/s)	1,571 ± 237	1,580 ± 214	1,673 ± 205	1,760 ± 199†
Group B (saline infusion)				
HR (bpm)	77 ± 18*	82 ± 18*	102 ± 18*	122 ± 18*
LVEDD (cm)	5.2 ± 0.6	5.2 ± 0.6	5.2 ± 0.6	5.1 ± 0.6
SAP (mm Hg)	146 ± 27	143 ± 33	145 ± 34	142 ± 33
LV dP/dt max (mm Hg/s)	1,505 ± 228	1,590 ± 268	1,795 ± 240*	2,050 ± 258*
Total saline given (ml)		83 ± 45	383 ± 121	666 ± 162

bpm = beats/min; HR = heart rate; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; SAP = systolic arterial pressure.

* $p < 0.05$ compared with the other 3 values.

† $p < 0.05$ compared with baseline and baseline +5 bpm.

diastolic filling is held constant by a rapid expansion of intravascular volume. The present study was performed to address these issues.

Methods

Patient population: Nineteen patients (3 men, 16 women), aged 33 to 68 years, referred for catheterization for the evaluation of chest pain were studied after they gave written informed consent. Beta-adrenergic blocking agents, calcium antagonists and long-acting nitrates were discontinued 24 hours before catheterization. Patients were studied in the fasting state after premedication with 10 mg oral diazepam. In each patient, left ventriculography demonstrated normal global and segmental LV function, and selective coronary arteriography demonstrated normal coronary arteries.

Experimental protocol: Thirty minutes after the completion of selective coronary arteriography, a bipolar pacing catheter was positioned in the high right atrium, and a micromanameter-tipped pigtail catheter (Millar Instruments) was placed in the left ventricle; the first derivative of LV pressure (dP/dt max) was then recorded. Systemic arterial pressure was measured continuously via a brachial or femoral arterial cannula. LV end-diastolic dimension was quantitated with targeted M-mode echocardiography using a Hewlett-Packard phased array 2-dimensional echocardiogram (model 77020 AC) with a 2.5-mHz transducer. Images were recorded on videotape for machine caliper measurement of end-diastolic dimension during saline infusion and on paper at 50 mm/s for later analysis. End-diastolic dimension was measured for 5 cardiac cycles at each heart rate and the values averaged. The measurements were taken at the tips of the papillary muscles, and these internal landmarks were used to ensure that measurements were performed consistently at the same anatomic location. End-diastole was defined at the peak of the R wave on a simultaneously recorded electrocardiogram.

LV end-diastolic dimension, systemic arterial pressure and dP/dt max were recorded at the patient's baseline heart rate. Then, atrial pacing was initiated at 5 beats/min above baseline rate. After 2 minutes of pacing, LV dimension, arterial pressure and dP/dt max were again recorded. These same variables were measured after 2 minutes of pacing at both 25 and 45 beats/min above the baseline rate to a maximal rate of 140 beats/min.

Before the experimental protocol was performed, each patient was randomly assigned to 1 of 2 groups. Group A received no saline infusion (n = 10); group B received saline infusion during pacing (n = 9). In the latter group, normal saline was rapidly administered (through a catheter in the femoral vein) to maintain a constant LV end-diastolic dimension.

Data analysis: Results are reported as mean ± 1 standard deviation. For groups A and B, the data for LV end-diastolic dimension, systolic arterial pressure and dP/dt max during the 4 heart rates (baseline, baseline +5 beats/min, baseline +25 beats/min, baseline +45 beats/min) were assessed with a repeated measures analysis of variance. The 2 groups were compared with Student *t* test.[17] For all analyses, a p value <0.05 was considered significant.

Results

Group A—Atrial pacing without saline infusion: For these 10 patients, LV ejection fraction averaged 0.71 ± 0.10 (range 0.51 to 0.85). As heart rate increased with atrial pacing, there was a stepwise decrease in LV end-diastolic dimension and a modest increase in dP/dt max (Table I). The individual responses of dP/dt max are shown in Figure 1. Systemic arterial pressure did not change significantly during atrial pacing. For these 10 individuals, the increase in LV dP/dt max with atrial pacing averaged 4.2 ± 5.1 (range −3.6 to +10.3) mm Hg/s/beat. From baseline to baseline +45 beats/min, dP/dt max increased 13 ± 16%.

Group B—Atrial pacing with saline infusion: For these 9 individuals, LV ejection fraction was 0.69 ± 0.10 (range 0.51 to 0.84). As heart rate increased with atrial pacing, LV end-diastolic dimension was main-

tained (by saline administration); systemic arterial pressure did not change significantly; and LV dP/dt max increased markedly (Table I, Figure 1). The increase in dP/dt max with atrial pacing averaged 12.3 ± 4.4 (range +6.2 to +19.7) mm Hg/s/beat, a significantly greater increase than that found in group A ($p = 0.002$). From baseline to baseline +45 beats/min dP/dt max increased 36 ± 17%, a greater increase than that noted in group A ($p = 0.007$).

Discussion

Previous studies in the conscious dog have shown that an increase in heart rate induces only a modest change in LV contractile performance, as reflected by dP/dt max. In 14 animals, Mahler et al[14] demonstrated a modest (16%) increase in LV dP/dt max as heart rate rose from 90 to 158 beast/min. In 10 animals, Higgins et al[13] measured LV dP/dt max and end-diastolic dimension during incremental atrial pacing. As heart rate increased, end-diastolic dimension decreased, and dP/dt max declined slightly (average 6%). Since the positive inotropic effect of a pacing-induced increase in heart rate may be offset by a decrease in LV diastolic filling (preload), these investigators[13] measured LV dP/dt max during incremental atrial pacing as LV diastolic dimension was held constant by the rapid infusion of saline. In these animals, dP/dt max increased by an average of 14%. In short, a pacing-induced increase in heart rate in the conscious dog appears to exert only a modest inotropic influence, even when LV preload is maintained by the rapid expansion of intravascular volume.

The inotropic effect of an increase in heart rate in man has not been well characterized. Gleason and Braunwald[16] measured LV dP/dt max in 3 patients with atrial septal defect before and after atropine. In these subjects, dP/dt max increased by 8.2 ± 4.7 mm Hg/s/beat (individual values, 11.2, 10.7 and 2.8). O'Brien et al[15] measured LV dP/dt max before and during atrial pacing in 7 patients with coronary artery disease; dP/dt max increased by 7.1 ± 13.6 (range −11.4 to +32.2) mm Hg/s/beat. In both of these studies, LV end-diastolic volume presumably fell as heart rate increased,[18] and this decrease in preload may have offset at least some of the positive inotropic effect of an increase in heart rate.

In the present study, we measured LV dP/dt max, end-diastolic dimension and systemic arterial pressure during incremental atrial pacing in 19 patients with normal LV function and coronary arteries. During atrial pacing alone, end-diastolic dimension decreased, systemic arterial pressure was unchanged and dP/dt max increased modestly (average increase 4.2 ± 5.1 mm Hg/s/beat, 13 ± 16%) (Table I, Figure 1). In contrast, in the 9 patients in whom saline was rapidly infused during atrial pacing to maintain a constant end-diastolic dimension, dP/dt max increased substantially (average increase 12.3 ± 4.4 mm Hg/s/beat, 36 ± 17%). The p values were 0.002 and 0.007, respectively, in comparison to those in whom pacing was performed without volume infusion) (Table I, Figure 1).

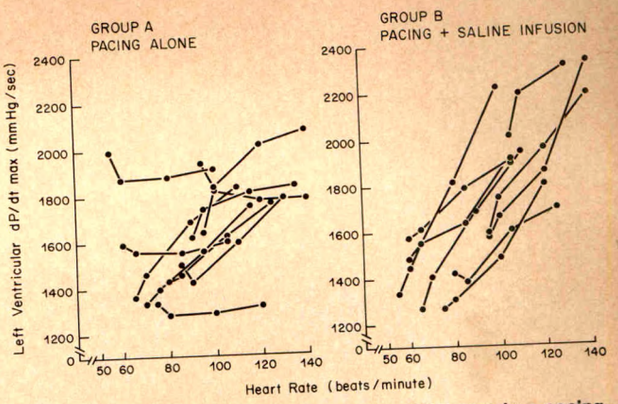

FIGURE 1. The response of left ventricular dP/dt max to a pacing-induced increase in heart rate in patients without (*left*) or with (*right*) the simultaneous infusion of saline (to maintain a constant left ventricular end-diastolic dimension). Each line represents the data from 1 patient. Left ventricular dP/dt max increased markedly during pacing-induced tachycardia in those given saline (*right*).

LV dP/dt max, a widely used index of myocardial contractility, is influenced by several factors.[12] An increase in heart rate, systemic arterial pressure or LV end-diastolic volume causes an increase in dP/dt max, whereas a decrease in these variables induces a decrease in dP/dt max.[16,19–21] In the present study, atrial pacing did not significantly alter systemic arterial pressure in those not given saline (group A) or those to whom saline was administered (group B) (Table 1). In those given saline, LV end-diastolic volume was held constant during incremental atrial pacing. Therefore, the observed increase in LV dP/dt max during pacing was due solely to the increase in heart rate.

During supine or upright exercise, LV end-diastolic volume and heart rate increase, and cardiac output rises.[22] Since LV preload is maintained or increases, the positive inotropic influence of exercise-induced tachycardia may contribute substantiallly to enhanced LV performance. Thus, the positive inotropic effect of an increase in heart rate is considerable if LV preload is maintained.

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Intrinsic Left Ventricular Contractility in Normal Subjects

MARVIN W. KRONENBERG, MD, JACK P. UETRECHT, MD, PhD, WILLIAM D. DUPONT, PhD, MICHAEL H. DAVIS, MD, BRIAN K. PHELAN, MD, and GOTTLIEB C. FRIESINGER, MD

The influence of autonomic tone on left ventricular (LV) contractility, along with the range of normal values and the effects of exercise on contractile state, were studied in 12 normal volunteers. Serial reproducibility was examined in a subgroup of 6. LV contractility was estimated by the LV peak-systolic pressure to end-systolic volume relation (pressure-volume relation), and the ratio of peak-systolic pressure to end-systolic volume (pressure/volume ratio). The cuff blood pressure and radionuclide ventriculogram were recorded at rest, during exercise and during pharmacologic pressure-afterloading with phenylephrine, before and after vagal and β-adrenergic "blockade." Both the pressure/volume ratio and ejection fraction increased during the stimulus of exercise (both $p \leq 0.008$). After blockade, the pressure-volume relations were highly linear ($r = 0.95 \pm 0.05$ [standard deviation], $n = 12$), and there was no systematic difference in their slopes induced by blockade. The serial studies of pressure-volume relations showed no significant differences. The results demonstrated that vagal and sympathetic tone were not important in the support of LV contractility in normal subjects at rest, and that the pressure-volume relation and pressure/volume ratio are reproducible between studies. Also, the findings confirmed that both the pressure/volume ratio and the ejection fraction were sensitive to exercise-induced changes in contractility. This demonstration of intrinsic LV contractility in normal subjects, plus the reproducibility of the measurements, supports the feasibility of serial study of LV contractility.

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The left ventricular (LV) end-systolic pressure-volume relation and variations have been employed as estimates of LV contractility.[1–12] However, there are few data to define the normal range of pressure-volume relations,[6,7,9–12] reproducibility[13,14] or effects of autonomic tone.[12,15] Autonomic tone might be important in setting the baseline ("intrinsic") contractile state, because the heart is richly innervated. Previously, Jose and Taylor[16] studied "intrinsic cardiac function" using atropine and propranolol to produce "autonomic blockade." In the present study, we employed the systolic pressure-volume concept and radionuclide ventriculography to evaluate "intrinsic LV contractility" in normal subjects at rest, during exercise and during autonomic blockade to assess the influence of autonomic tone. The reproducibility of the data was investigated.

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Address for reprints: Marvin W. Kronenberg, MD, Cardiology Division, Vanderbilt University School of Medicine, Nashville, Tennessee 37232.

Methods

Population and protocol: We studied 14 normal volunteers. They were untrained, asymptomatic adults (9 men, 5 women), ages 33 ± 12 years (standard deviation), range 21 to 69. Each had a normal physical examination, took no medications and gave written informed consent on forms approved by our institutional review board. Serial studies were performed in 9.

Intravenous cannulae were inserted in right and left forearm veins for blood sampling and drug infusion, respectively. The subjects lay supine and were studied while fasting. Radionuclide ventriculograms were collected to estimate LV volume (see later) and auscultatory blood pressure was measured simultaneously using an 8-stage protocol (Figure 1). Data were collected at rest (stage 1), during supine bicycle ergometer exercise (stage 2) and after a recovery period of 20 to 30 minutes following exercise (stage 3). Then, the systolic blood pressure was increased in steps by a phenylephrine infusion (stages 4 and 5). After discontinuing phenylephrine, atropine and propranolol were infused intravenously to produce vagal and β-adrenergic "blockade." Loading doses were followed by maintenance infusions. Data were reacquired when the systolic pressure was stable (stage 6). Then, the phenylephrine infusion was repeated to achieve 2 pressure increments and measurements were repeated (stages 7 and 8). The protocol required 3 hours, with 45 minutes for stages 6 through 8.

Imaging: Red blood cells were labeled in vivo[17] using 25 mCi technetium-99m pertechnetate. Electrocardiographic R-wave gated images of the cardiac blood pool in the left anterior oblique projection were collected by a PhoGamma IV scintillation camera (Siemens) using a low-energy all-purpose collimator and a symmetrical 20% window. They were stored by a PDP 11/40 computer (Digital Equipment), using a 64 × 64 image matrix, 30 ms per frame, 20 frames per cardiac cycle and variable hardware zoom for magnification. Images were collected for 2 million counts at rest (usually 5 minutes) and for 3 minutes on exercise. For estimating LV volume, with each image a 5-ml blood sample was drawn intro a heparinized syringe, transferred to a Petri dish using a pipette with 0.5% error at full scale (Oxford Macro-Set, Sherwood Medical), placed on the collimator and counted for 5 minutes afterwards.

Blood pressure was assessed once a minute during imaging with an ameroid cuff sphygmomanometer.

Drug infusion: Phenylephrine was infused with a calibrated pump (Harvard). After the initial rate of 0.2 μg/kg/min, the rate was increased to achieve an approximate 20 mm Hg increment in systolic pressure. Then, the radionuclide ventriculogram was repeated and the rate increased for a similar pressure increment before another image. This sequence was repeated after vagal and β-adrenergic "blockade."[16] For this, atropine (0.2 mg/ml) was infused over 10 to 15 minutes to a total loading dose of 0.04 mg/kg. The maintenance dose was 0.2 μg/kg/min. Propranolol was infused simultaneously, totalling 0.2 mg/kg. The maintenance dose was 1.1 μg/kg/min.

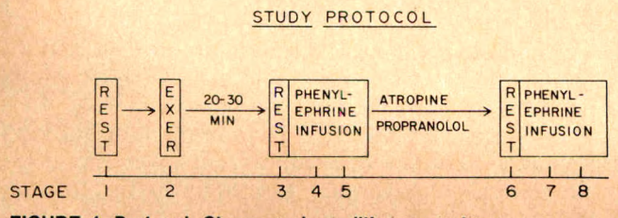

FIGURE 1. Protocol. Stages and conditions are shown.

Exercise protocol: Exercise was performed by pedaling a bicycle ergometer (Collins), supine at 60 rpm, beginning at 25 watts and increasing over 2 to 3 minutes to an individualized maximal load for a 3-minute exercise image.

Serial studies: Two weeks to 3 months later, a second study was performed in 9 subjects following an identical protocol. All subjects able to return were studied without reference to their initial evaluation.

Radionuclide ventriculography: We evaluated this method for estimating the LV ejection fraction and volume using software of our design.[18] Among 18 patients, the correlation for ejection fraction between radionuclide and contrast ventriculography was 0.93 ($p < 0.001$).[19] In 9 other patients, the correlation between radionuclide and contrast LV volume was 0.94 ($n = 18$, $p < 0.001$) (combining end-diastole and end-systole), where contrast = 3.16 + 4.54 (radionuclide) using the method of Dehmer et al.[19]

Reproducibility: In a wide variety of 50 radionuclide ventriculograms, intraobserver variability for end-systolic volume (ml) in duplicate trials was <2% (difference not significant) with close correlation ($r = 0.99$, $p < 0.001$; trial 1 = 0.67 + 0.97 × trial 2). In 47 studies analyzed by 2 observers independently, interobserver variability for end-systolic volume was 3% (difference not significant) with close correlation ($r = 0.99$, $p < 0.001$; observer 1 = −1.54 + 1.05 × observer 2). There were equally close intra- and interobserver results for end-diastolic volume and ejection fraction with correlation coefficients >0.98.

Blood pressure: In 9 consecutive catheterized patients there was close correlation between the systolic blood pressure (mm Hg) by cuff and in the ascending aorta (cuff = −1.68 + 1.03 × aortic) ($r = 0.991$, $p < 0.001$).

Data analysis: The 5 systolic and diastolic pressures during each radionuclide ventriculogram were averaged.

Radionuclide ventriculograms were analyzed in duplicate for end-diastolic volume, end-systolic volume and ejection fraction.

Pressure-volume relations were evaluated by 2 methods. First, the relation of peak-systolic pressure to LV end-systolic volume (pressure-volume relation) was assessed before and during phenylephrine infusions, both before and after autonomic blockade (stages 3 to 5 and 6 to 8). The pressure-volume data were graphed and examined by linear regression analysis. The slope, the standard error of the slope estimate and the extrapolated value of end-systolic volume at a systolic pressure of zero were tabulated. Second, the ratio of peak-systolic pressure to LV end-systolic volume (pressure/volume ratio) was calculated at rest and during exercise.

Repeated measurements and duplicate data were examined by analysis of variance, paired t tests and linear regression, as appropriate. Statistically significant differences were defined as $p < 0.05$.

Results

Fourteen subjects had 1 study and 9 subjects had 2. Studies were excluded only for inadequate definition of the left ventricle, artifacts in blood sample counts or inadequate exercise electrocardiographic gating. For study 1, there were technically excellent rest-exercise pressure/volume ratios for 13 subjects and pressure-volume relations for 12. For study 2, there were pressure/volume ratios and pressure-volume relations for 6.

Rest-exercise results: In study 1 the pressure/volume ratio increased from 3.6 ± 2.7 mm Hg/ml "units" at rest to 7.9 ± 3.5 during exercise (n = 13, p <0.001) (Figure 2A, Table I). We compared the reproducibility of the pressure/volume ratios of studies 1 and 2 (Figure 2B). There were no significant differences in the group data of pressure/volume ratios at rest or during exercise, but for individuals the ratios differed by <3.2 units at rest and <2.5 units during exercise.

Pressure-volume relations: The average increment in systolic pressure between stages was 22 mm Hg. Before blockade, the average heart rate slowed as the pressure increased, from 80 at stage 3 to 56 at stage 4 and to 49 at stage 5. After blockade, the heart rate averaged 109 during stage 6 and 114 during stage 8. Systolic blood pressure was 153 ± 12 mm Hg in stage 5 and 159 ± 12 mm Hg in stage 8 (p = 0.04). The phenylephrine infusion rate averaged 1.3 μg/kg/min in stage 4 and 2.2 in stage 5, but only 0.8 in stage 7 (p <0.001 vs stage 4) and 1.1 in stage 8 (p <0.002 vs stage 5). The plasma propranolol concentration was measured 8 times in 7 subjects at the beginning and end of the maintenance infusion (45 minutes). The initial level was 80 ± 25 ng/ml and the final level 77 ± 18 ng/ml (difference not significant).

Figure 3 illustrates 2 general patterns of pressure-volume relations before and after blockade. In panel A the relations were linear before and after blockade (subject 8), but panel B shows a marked leftward shift of the pressure-volume relation before blockade (subject 11) at the higher dose of phenylephrine. Figure 4 displays the pressure-volume relations for all 18 studies in the 12 subjects, before and after blockade. We inspected these curves for linearity, after excluding 2 (subject 1, study 1, preblockade; subject 4, study 1, postblockade). Of these 2, the first had a very small pressure change and the second had only 2 points for analysis since phenylephrine was discontinued because of headache. Of the remaining 16, before blockade, 7 were linear but 9 showed a leftward shift at the highest pressure. After blockade, only 2 showed such a leftward shift. The difference in linearity before and after blockade was significant (p = 0.02).

Table II lists the pressure-volume relations for studies 1 and 2. The pressure-volume relations after blockade were estimated from stages 6 through 8. There were 3 data points for 11 of 12 subjects, and the r values of their pressure-volume slopes were linear, averaging 0.95 in study 1. Slopes before blockade were estimated from stages 3 and 4. This avoided the nonlinearity in stage 5, assumed to be due to β-adrenergic stimulation. In study 1, the slope before blockade was 2.2 ± 1.1 mm Hg/ml (n = 12); after blockade it had become 2.5 ± 1.6. These values were not significantly different. In that study, the extrapolated end-systolic volume for a systolic pressure of 0 averaged −30 ml before blockade and −28 ml after it. These values were not significantly different. In study 2, the extrapolated volume averaged −28 ml before blockade and −6 ml after (p = 0.051), approaching, but not achieving standard statistical significance.

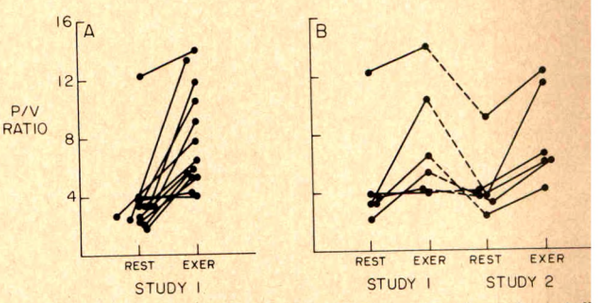

FIGURE 2. Pressure/volume ratio. *A*, the ratio of peak-systoli pressure to end-systolic volume increased on exercise. *B*, duplicat rest and exercise ratios were not significantly different in seri studies. The maximum difference in the exercise pressure/volum ratio was 2.5 units. P/V = pressure/volume.

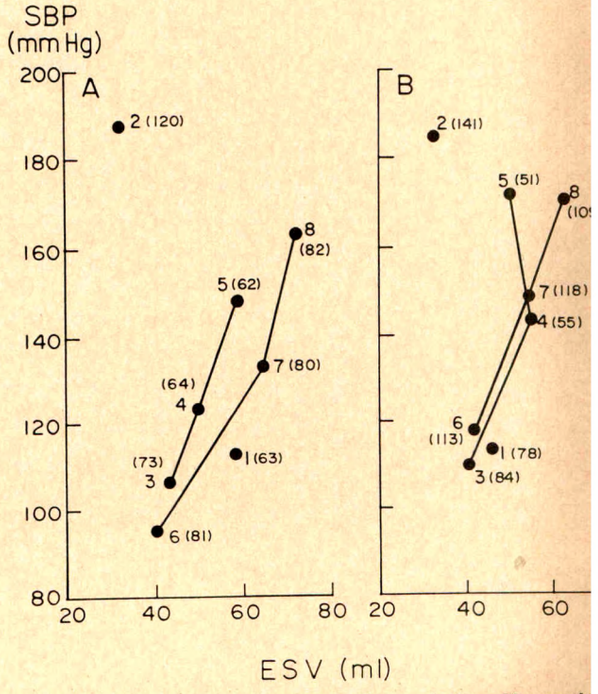

FIGURE 3. Two patterns of pressure-volume relations. The numb 1 through 8 denote stages in the protocol and the numbers parentheses represent heart rate. *A*, subject 8: the systolic pr sure-volume relation was linear before and after blockade. *B*, s ject 11: there was a marked leftward shift in the pressure-volu relation with a higher infusion rate of phenylephrine before au nomic blockade. The relation was more linear after blockade

TABLE I Peak Systolic Blood Pressure and End-Systolic Volume at Rest and During Exercise

		Study 1											Study 2										
		Rest					Exercise						Rest					Exercise					
Subject	Sex	SBP (mm Hg)	ESV (ml)	P/V	EF (%)	HR (bpm)	SBP (mm Hg)	ESV (ml)	P/V	EF (%)	HR (bpm)	ΔP/V	SBP (mm Hg)	ESV (ml)	P/V	EF (%)	HR (bpm)	SBP (mm Hg)	ESV (ml)	P/V	EF (%)	HR (bpm)	ΔP/V
1	F	111	9	12.3	84	66	168	12	14.0	85	158	1.7	109	12	9.1	85	65	160	13	12.3	85	151	3.2
2	M	125	37	3.4	70	75	198	19	10.4	84	167	7.0	124	34	3.7	72	68	194	17	11.4	87	130	7.7
3	F	106	27	3.9	73	56	150	38	4.0	66	176	0.1	103	29	4.0	73	67	157	24	6.5	80	155	2.5
4	F	107	29	3.7	61	73	158	39	4.1	64	179	0.4	110	31	3.6	65	93	159	26	6.1	72	184	2.5
5	F	100	45	2.2	71	55	167	31	5.4	80	148	3.2	102	31	3.3	76	54	165	27	6.1	80	142	2.8
6	M	126	38	3.3	72	70	146	23	6.3	79	117	3.0	124	52	2.4	62	61	150	37	4.1	70	114	1.7
7	M	106	31	3.4	68	56	178	15	11.9	83	155	8.5											
8	M	113	57	2.0	53	63	188	32	5.9	66	127	3.9											
9	M	105	32	3.3	72	46	199	22	9.1	83	138	5.8											
10	M	112	67	1.7	65	56	178	33	5.4	74	140	3.7											
11	M	114	46	2.5	64	78	185	33	5.6	80	141	3.1											
12	M	116	48	2.4	64	77	188	14	13.4	84	170	11.0											
13	M	111	42	2.6	67	60	170	22	7.7	81	145	5.1											
Mean (n = 13)		112	39	3.6	68	64	175*	26*	7.9*	78*	151*	4.3											
SD		8	15	2.7	7	10	17	9	3.5	8	19	3.2											
SE		2	4	0.8	2	3	5	3	1.0	2	5	0.9											
Mean (n = 6)		113	31	4.8	72	66	165*	27	7.4	76	158*	2.6	112	32	4.3	72	68	164*	24†	7.8†	79†	146*	3.4
SD		11	13	3.7	7	9	19	11	4.0	9	23	2.6	10	13	2.4	8	13	15	8	3.3	7	24	2.2
SE		4	5	1.5	3	4	8	4	1.6	4	9	1.0	4	5	1.0	3	5	6	3	1.4	3	10	0.9

* $p \leq 0.003$ rest versus exercise; † $p < 0.05$ rest versus exercise.

Bpm = beats per minute; EF = ejection fraction; ESV = end-systolic volume; HR = heart rate; P/V = ratio of SBP/ESV; ΔP/V = change in P/V ratio; SBP = peak-systolic blood pressure; SD = standard deviation; SE = standard error.

TABLE II End-Systolic Pressure-Volume Relations

	Study 1						Study 2					
	Pre-blockade		Post-blockade				Pre-blockade		Post-blockade			
Subject	m	V_0	m	V_0	r	SE	m	V_0	m	V_0	r	SE
1	1.0	−104	2.7	−35	0.96	0.75	1.6	−64	2.8	32	0.98	0.56
2	1.9	−31	2.3	−15	0.87	1.32	3.5	−5	2.8	−16	0.99	0.43
3	1.5	−37	2.8	−12	0.85	2.23	1.8	−30	4.2	3	0.98	0.89
4	3.6	1	1.1	−58	—	—	1.6	−49	3.1	−8	0.99	0.28
5	0.7	−108	1.6	−36	0.99	0.23	5.0	9	4.1	11	0.92	1.72
7	4.3	0	6.8	17	0.93	2.77	1.9	−26	3.7	8	0.99	0.35
8	3.4	12	1.9	−9	0.97	0.50						
9	2.8	5	3.3	−3	1.	0.02						
10	2.4	−11	1.6	−38	0.99	0.10						
11	2.4	−6	2.5	−6	0.99	0.12						
12	1.3	−49	0.8	−104	0.96	0.24						
13	1.9	−32	2.0	−41	0.97	0.46						
Mean (n = 12)	2.2	−30	2.5	−28	0.95	0.79						
SD	1.1	40	1.6	32	0.05	0.93						
SE	0.3	12	0.5	9	0.02	0.28						
Mean (n = 6)	2.2	−47	2.9	−23	0.92	1.46	2.6	−28	3.5	−6	0.98	0.71
SD	1.5	49	2.0	26	0.06	1.04	1.4	27	0.6	16	0.03	0.51
SE	0.6	20	0.8	11	0.03	0.47	0.6	11	0.3	7	0.01	0.22

M = slope of linear regression of end-systolic pressure-volume relations; r = Pearson correlation coefficient; SE = standard error of estimate; V_0 = ESV when SBP equals 0. Values were not significantly different by paired *t* tests.

Reproducibility of pressure-volume relations: Pressure and volume were reproducible after autonomic blockade in the group of 6 serial studies (Figure 5). The individual pressure-volume data were quite similar visually (Figure 4), and statistically (Table II). There were no significant differences in the pressure-volume slopes either before or after blockade, or in the volumes at zero-pressure. Also, the 95% confidence limits of the standard error of the slope estimates after blockade overlapped in every case.

Discussion

End-systolic pressure volume relations reflect LV contractility.[1–7,10–13] We examined peak systolic pressure to end-systolic volume relations to assess in normal volunteers the importance of autonomic tone, the effects of exercise and the reproducibility of the data. We found no significant effect of autonomic tone on systolic pressure-volume relations or on pressure/volume ratios; reproducibility was generally good. The pressure/volume ratio increased during exercise, reflecting increased contractility.

Pressure-volume relations and pressure/volume ratio: The slope of the LV end-systolic pressure-volume relation equals the end-systolic pressure divided by the difference of the end-systolic volume minus a correction factor (the volume at zero pressure, termed V_0).[2] Suga et al[1] and Sagawa et al[8] proposed the pressure/volume ratio as an estimate of contractility. This ratio may be considered as 1 related locus of the pressure-volume relation, but its absolute value differs from the slope value because of V_0.

In the isolated heart, LV volume is altered by a compliant balloon. There, the systolic pressure-volume relation is linear and the V_0 usually has a positive value.[2,20] However, V_0 has yet to be determined directly in vivo. We confirmed that systolic pressure-volume relations were linear, but the extrapolated V_0 was usually negative. This value has been reported both as positive[3,4,6,7,21] and negative.[5,21] Such extrapolation assumes linearity, but negative values imply nonlinearity below the operating range. Thus, extrapolation of V_0 may be invalid and greater reliance should be placed on actual pressure and volume measurements.

The pressure/volume ratio may change by altering pressure, volume, or both. An increase in pressure coupled to a decrease in volume is consistent with increased contractility, and this occurred during exercise in our study.

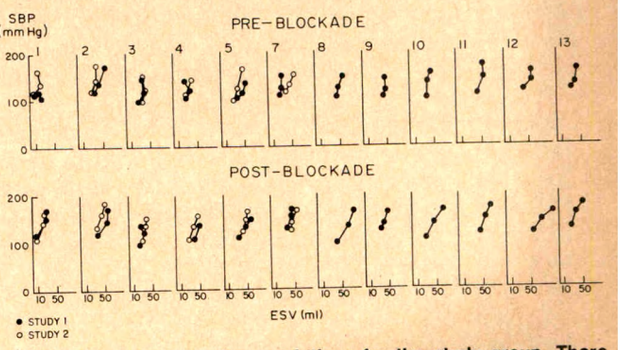

FIGURE 4. Pressure-volume relations for the study group. There was an overall similarity. Serial studies in 6 subjects were generally concordant. Data were more linear after autonomic blockade for reasons explained in the text. Numbers above graphs specify subjects as listed in tables.

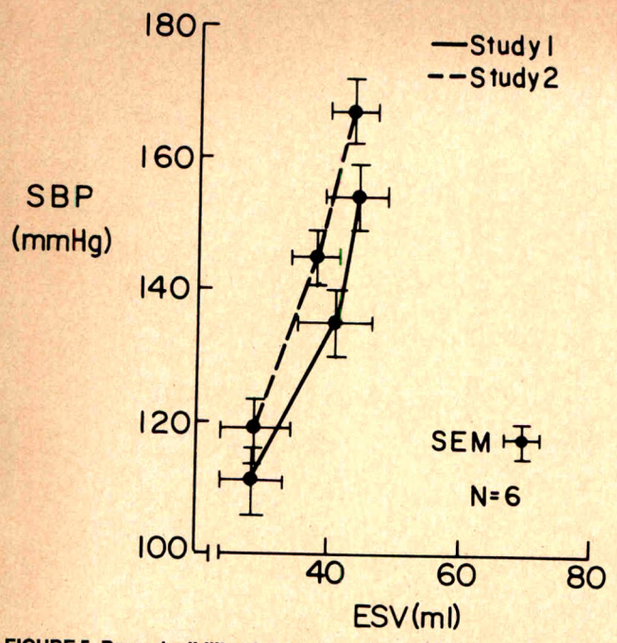

FIGURE 5. Reproducibility of pressure-volume relations. Stages 6 to 8 of studies 1 and 2 are shown. The mean pressure and volume were not significantly different.

Autonomic blockade: Whereas others have examined contractility in transplanted hearts (denervated),[12,22] the present study used a more direct approach by investigating the effects of autonomic tone on LV contractility and reproducibility in normal subjects. There was no difference in the slope of the pressure-volume relation before or after blockade after excluding stage 5, which was probably affected by phenylephrine's β-adrenergic effect.[23,24] Resting autonomic tone seems relatively unimportant for supporting normal LV contractility in dogs.[3] There are fewer data in normal humans. Borow et al found no differences between pressure-dimension relations in transplanted denervated hearts and in other normal subjects.[12] Crawford et al found that end-systolic dimension was unchanged before and after oral propranolol.[15] However, in heart failure,[16] cardiac output decreased after blockade but not in normal subjects. Thus, sympathetic drive may support contractility in heart failure, but not in the normal population.

Reproducibility: The duplicate, serial pressure-volume relations in 6 subjects were not significantly different. The greatest difference between duplicate pressure/volume ratios during exercise was 2.5 units and may represent the upper limit of normal variability.

Potential limitations included the volume and blood pressure methods, the effect of heart rate and drugs. The radionuclide method is affected by attenuation[25-27], but can quantitate volume,[3,19,25-27] small changes in volume,[27] pressure-volume loops[28] and pressure-volume relations.[27] Changes in the same subject should be assessed reliably, because attenuation should be constant.

Using 3 points per pressure-volume curve and peak systolic pressure might cause errors. Although there are problems in using 3 points to define linearity, other studies have proven this point.[1-3,5-8,10-14,20,21,27,29] Estimates of contractility by peak and end-systolic pressure are quite similar,[4,5,21,29] but the former has steeper slopes.

Tachycardia is a moderate, positive inotropic stimulus[22,30,31] and may decrease end-systolic volume.[22,28] In our study, the mean heart rate increased 29 beats from stage 3 to 6, but in 1 of our subjects a 40-beat increase did not affect pressure-volume relations in further studies (data not shown). Baroreceptor-mediated bradycardia (as before blockade) has not been studied, but when pacing stops, end-systolic volume[22] and end-systolic dimension[30] change minimally. Reflexes, hormonal background and coronary perfusion pressure might modify the effect of rate alone.[31] The available data favor our conclusion that vagal and β-adrenergic stimuli do not significantly alter normal LV contractility.

Phenylephrine has cardiac β-adrenergic effects[23,24] and our data confirm this in some subjects (Figures 3 and 4). Less phenylephrine was required to raise the blood pressure after blockade, probably by attenuating β-adrenergic vasodilation.[32] β-adrenergic blockade seems necessary before using phenylephrine. Although methoxamine might be as useful,[33] it also may affect contractility.[24,34,35]

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Strategies for Increasing Early Adherence to and Long-Term Maintenance of Home-Based Exercise Training in Healthy Middle-Aged Men and Women

ABBY C. KING, PhD, C. BARR TAYLOR, MD, WILLIAM L. HASKELL, PhD, and ROBERT F. DEBUSK, MD

Two studies were undertaken to compare strategies for the adoption and maintenance of moderate-intensity, home-based exercise training. In the study of adoption, 52 men and women who had served for 6 months as controls for a study of moderate-intensity, home-based exercise training received 30 minutes of baseline instruction. They were then randomized to receive continuing instruction and support through 10 staff-initiated telephone contacts of 5 minutes each every 2 weeks, or to receive no telephone contacts. In subjects receiving telephone contacts, peak oxygen uptake increased significantly after 6 months, whereas no increase was observed in subjects receiving no staff support ($p < 0.05$). In the maintenance study, 51 men and women who had significantly increased their peak oxygen uptake by 6 months of moderate-intensity, home-based exercise training were randomized to undergo daily self-monitoring and receive adherence instructions, or undergo weekly self-monitoring only, during a second 6-month period of training. Subjects performing daily self-monitoring reported completing significantly more exercise training sessions during the 6 months of training than subjects performing weekly self-monitoring; functional capacity in both groups remained higher than before training ($p < 0.05$). Taken together, these studies suggest that brief baseline instruction followed by continuing telephone contact with staff can be used to help people adopt a moderate-intensity, home-based exercise training program that can be maintained by simple self-monitoring strategies.

(Am J Cardiol 1988;61:628–632)

Despite the known health benefits of regular physical activity,[1,2] most American adults continue to remain quite inactive.[3] This is particularly true for middle-aged and older men and women.[4,5] Factors influencing participation in physical activity include the type of activity, its intensity, frequency, and level of discomfort, convenience, perceived risk and enjoyment associated with it.[6] Surveys indicate that many people prefer moderate-intensity activities such as brisk walking as opposed to more vigorous activities,[3] and those they can perform individually rather than in a structured setting.[7] Significant increases in functional capacity have been achieved in healthy individuals[8,9] through home-based exercise training with medical supervision provided by telephone and mail contact. Studies show that home-based exercise training at low to moderate intensity (60 to 75% of the peak heart rate)[8] and moderate intensity (65 to 77% of the peak heart rate)[9] fits these preferences and significantly increases the functional capacity of healthy middle-aged persons.

The present study was designed to evaluate strategies for enhancing the adoption and maintenance of exercise training by healthy middle-aged participants in a 6-month randomized trial of home-based exercise training.[9] The level of adoption of exercise was evaluated over a 6-month period in subjects who had served as controls during the preceding 6 months of the randomized trial. The maintenance of exercise was evalu-

From the Departments of Medicine and Psychiatry, Division of Cardiology, Stanford Center for Research and Disease Prevention and Stanford Cardiac Rehabilitation Program, Stanford University School of Medicine, Stanford, California. This work was supported by a grant awarded to Dr. DeBusk by the PepsiCo Foundation, Purchase, New York, and by grant 36272 awarded to Dr. Haskell by the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received November 2, 1987; revised manuscript received and accepted November 9, 1987.

Address for reprints: Abby C. King, PhD, 730 Welch Road, Palo Alto, California 94304.

ated over a 6-month period in subjects who had undergone exercise training in the preceding 6 months of the randomized trial. Adoption and maintenance studies included 2 levels of intervention.

Adoption: One group of subjects in the adoption study received support and guidance through regularly scheduled phone contacts by project staff and 1 group received no such support and guidance.

Maintenance: One group in the maintenance study was instructed in daily self-monitoring of activity and 1 group was instructed in weekly self-monitoring.

Methods

Participants were 52 and 51 healthy men and women, ages 49 ± 6 and 47 ± 5, respectively, employed at Lockheed Missiles and Space Corporation in Sunnyvale, California. They had previously participated in a 6-month randomized, controlled trial to evaluate the physiologic effects of moderate-intensity, home-based exercise training.[10] Eligibility for the original trial included age 40 to 60, <25% overweight based on 1959 Metropolitan Life Insurance tables and absence of major musculoskeletal problems, overt cardiopulmonary disease or cardiac medications. At the end of the 6-month trial, the 52 control subjects and 51 training subjects completing Phase I were invited to participate in the Phase II trial (Figure 1).

Adoption study: The 26 men and 26 women participating in the adoption study received instructions for moderate-intensity, home-based exercise training similar to those provided to participants in the Phase I training study. Exercise training was at a heart rate 65% of that achieved during symptom-limited treadmill exercise testing plus 20 beats, 4 times per week and 30 minutes per session. Subjects were oriented to the home-based training program by the project staff in a 15-minute face-to-face session which followed participants' viewing of a 15-minute videotape on exercise training. Subjects used a portable heart rate monitor (Pacetron, Neuromedics) to assist them to remain within the prescribed training heart rate range. This monitor, which used electrodes strapped to the chest, emitted an audible tone when the heart rate was above or below the prescribed training range.

All participants were instructed in self-directed behavioral strategies that would aid them to exert better control over their exercise. These included relapse-prevention strategies[11,12] to limit the negative impact of missed sessions on subsequent adherence. They were taught to identify high-risk situations leading to breaks in their exercise regimen and to avoid or cope with such breaks. They were instructed in daily self-monitoring of exercise including the frequency and duration of exercise, ratings of perceived exertion during exercise using the Borg Scale[10] and of the enjoyment and convenience of the exercise sessions. These daily monitoring logs were mailed to the staff once each month.

The staff spoke on the phone with the 14 men and 15 women randomized to adoption-condition 1 to discuss the progress of their exercise program and to offer support and guidance (Table I). An average of 10 such telephone contacts averaging 5 minutes each was made within the 6-month training period.

The 12 men and 11 women randomized to adoption-condition 2 received the same instruction and follow-up as participants in condition 1, except that regular staff-initiated telephone contact was omitted (Table I). Participants in both conditions with >2 week overdue exercise logs received a reminder telephone call from a staff member.

Maintenance study: The 26 men and 25 women participating in the maintenance study received instructions for moderate-intensity home-based exercise training identical to those provided to participants in the adoption study. Self-monitoring was the principal strategy for maintaining adherence. The 13 men and 15 women randomized to condition 1 were instructed in daily monitoring of the frequency, duration, intensity and perceived enjoyment and convenience of their exercise sessions. They completed exercise logs which

TABLE I Procedures to Enhance Adoption

Condition 1 and Condition 2	Condition 1 Only
Daily exercise log (returned monthly)	Staff phone contacts (support and guidance)
Telephone prompt if exercise log not returned	
Relapse prevention instruction	
Adherence tips and guidelines	
Self-test chart	

TABLE II Procedures to Enhance Maintenance

Condition 1	Condition 2
Daily exercise log (returned monthly)	Weekly exercise log (returned quarterly)
Telephone prompt if exercise log not returned	Telephone prompt if exercise log not returned
Adherence tips and guidelines	

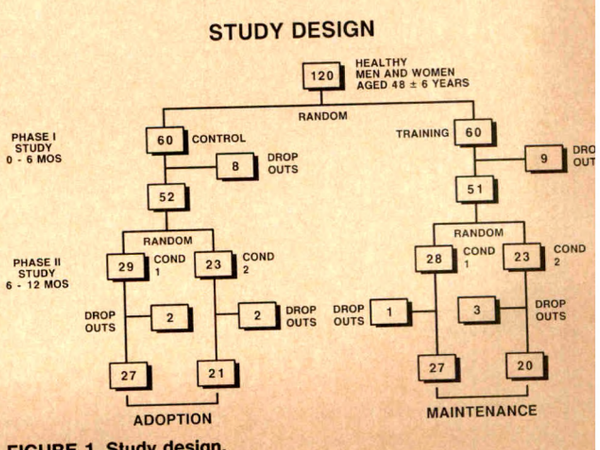

FIGURE 1. Study design.

TABLE III Peak Oxygen Uptake at Baseline, 6 Months and 12 Months for Adoption and Maintenance Studies

		Mean VO_2 Max (ml/kg/min)		
	n	Baseline	6 mo	12 mo
Adoption study				
Condition 1 (phone contacts)	27	30 ± 6	30 ± 6	32 ± 7*
Condition 2 (no phone contacts)	21	30 ± 5	30 ± 6	31 ± 6
Maintenance study				
Condition 1 (daily monitoring)	27	29 ± 6	33 ± 6	31 ± 6
Condition 2 (weekly monitoring)	20	30 ± 5	33 ± 6	32 ± 6

* Comparison between conditions 1 and 2, $p < 0.05$.
VO_2 = peak oxygen uptake.

were mailed to the staff each month. They also received a list of adherence tips and guidelines. The 13 men and 10 women randomized to maintenance condition 2 were instructed in weekly monitoring of the frequency, duration and intensity of their exercise sessions. These individuals completed exercise logs and returned them every 3 months (Table II).

Laboratory evaluation: The laboratory evaluation, conducted at baseline and 6 and 12 months afterwards, was identical for all participants. It included a symptom-limited treadmill exercise test with monitoring of blood pressure, electrocardiogram, rating of perceived exertion and measurement of oxygen consumption.[9]

Statistical analysis: Unpaired *t* tests were used to compare differences in the changes between groups. Paired-comparison *t* tests were used to compare differences within groups. Five percent 2-tailed *t* tests were used.

Results

Adoption study: Regarding self-reported adherence, the number of exercise sessions reported on the monthly exercise logs during the 6-month period was 12.4 ± 6 for condition 1 and 9.8 ± 8 for condition 2 (not significant). The duration of reported exercise sessions in conditions 1 and 2 was 32 ± 6 and 28 ± 10 minutes, respectively (not significant). There were no sex differences in either frequency or duration of exercise.

Changes in peak oxygen uptake: Twenty-seven of the 29 condition 1 participants (93%) and 21 of the 23 condition 2 participants (91%) returned for treadmill testing at the end of the 6-month adoption period (Figure 1). Values of peak oxygen uptake (VO_2 max) at 12 months were 8% and 2% higher than at 6 months in subjects of condition 1 and 2, respectively ($p < 0.05$) (Figure 2). The increase in VO_2 max was similar for men and women. Values of VO_2 max throughout Phases I and II of the study are shown in Table III.

Correlations between self-reported adherence and changes in peak oxygen uptake: The change in VO_2 max was significantly correlated with self-reported adherence to exercise training. Pearson product moment correlations were $r = 0.54$ for the number of exercise sessions per month ($p < 0.001$) and $r = 0.38$ for the average rating of perceived exertion per exercise session ($p < 0.002$). The number of sessions reported was significantly correlated with the rated enjoyment of the sessions ($r = 0.46$, $p < 0.01$) and with the rated convenience of exercise ($r = 0.40$, $p < 0.01$).

Maintenance study: Data on self-reported adherence showed that the number of reported exercise sessions per month during the 6-month period was 11.4 ± 6 for condition 1 subjects and 7.5 ± 6 for condition 2 subjects ($p < 0.01$). There was no sex difference in frequency or intensity of exercise. Mean duration of exercise sessions for condition 1 was 37 ± 9 minutes.

Changes in peak oxygen uptake: Twenty-seven of the 28 condition 1 participants (96%) and 20 of the 23 condition 2 participants (87%) returned for treadmill testing at the end of the 6-month maintenance period (Figure 1). Values of VO_2 max at 12 months were 4% and 5% lower than at 6 months in subjects of condition 1 and 2, respectively (both $p < 0.05$) (Figure 3). The values of VO_2 max at 12 months exceeded those at

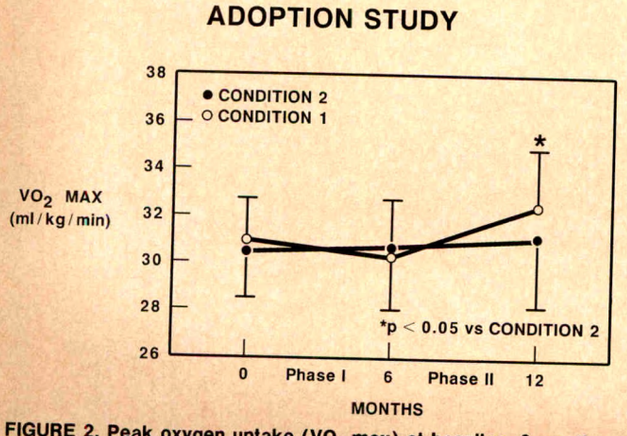

FIGURE 2. Peak oxygen uptake (VO_2 max) at baseline, 6 months and 12 months by adoption condition.

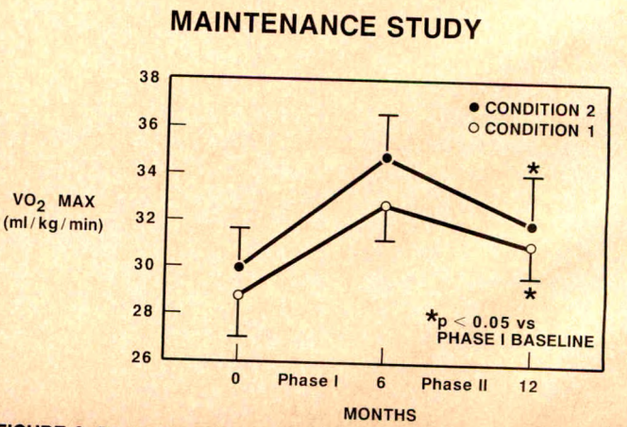

FIGURE 3. Peak oxygen uptake (VO_2 max) at baseline, 6 months and 12 months by maintenance condition.

baseline by 8% ($p < 0.001$) and 7% ($p < 0.04$) in condition 1 and 2 subjects, respectively. Values of VO_2 max throughout phases I and II of the study are shown in Table III.

Correlations between self-reported adherence and changes in peak oxygen uptake: Change in VO_2 max was significantly correlated with the number of exercise sessions reported per month ($r = 0.31$, $p < 0.05$). Ratings of the enjoyment of sessions were positively related to the reported duration of sessions ($r = 0.50$, $p < 0.005$) and the perceived convenience of exercise sessions ($r = 0.60$, $p < 0.005$).

Discussion

This was 1 of the first studies to systematically evaluate factors influencing the adoption and maintenance of exercise over a 6-month period. The behavioral strategies for enhancing the adoption of exercise included goal-setting, self-monitoring, instruction in relapse prevention and supportive feedback provided by telephone contact with staff. Gains achieved during the first 6 months were maintained over the second 6 months by self-directed monitoring and relapse prevention.

In the adoption of exercise, the first 6 months are considered crucial.[13,14] The results of the present study reveal that a home-based, individually prescribed program of moderate-intensity exercise accompanied by regularly scheduled staff phone contacts is associated with a high degree of adherence and a significant increase in peak oxygen uptake in healthy middle-aged individuals. Participants in the adoption study received an average of 30 minutes of initial face-to-face instruction by staff and <60 minutes of subsequent phone contact with staff during the entire 6-month period. In contrast, group-supervised exercise training programs usually entail 72 hours of face-to-face contact over a similar period.[15]

The adoption of a new health behavior such as physical exercise requires the mastery of new skills. In addition to increasing their activity gradually, so as to avoid excessive fatigue and injury, individuals need to learn how to restructure their environment to support the new activity. This entails changing time schedules, adjusting to the sensations generated by aerobic activity, such as perspiration and increased heart rate and breathing, and altering attitudes that impede participation such as the belief among some women that perspiring is "unladylike" and hence undesirable.

Social support is often important in the early stages of adoption, when the benefits of exercise have yet to be experienced and activity-related discomfort is at its peak.[12] However, this need not require prolonged personal contact, for telephone contact is a convenient alternative.[8,9] In the adoption study, only the subjects who received supportive telephone contact from the staff significantly increased their oxygen uptake.

Strategies to maintain adopted exercise patterns differ from those used to promote the adoption of exercise habits.[16,17] In the current study, maintenance procedures were largely *self-directed* rather than *staff-directed*. Individuals monitored their own progress and implemented relapse prevention strategies when their exercise efforts began to slacken. This model of ongoing self-regulation has been utilized by Bandura and Simon to counteract relapse in obesity.[18]

Subjects in the maintenance study reported a high rate of adherence to exercise and exhibited a peak oxygen uptake at 12 months that exceeded that at the beginning of the Phase I study. However, adherence tips and guideline provided to subjects in condition 1 did not maintain their peak oxygen uptake at levels higher than those of subjects in condition 2. Both groups of subjects appear to have mastered relapse-prevention strategies during the 6-month adoption phase preceding the maintenance study.

In many group-based exercise programs the dropout rate at 6 months approaches 50%.[19] Apparently the inconvenience of attending a class may outweigh the advantages of information and support provided by the group. We found that convenience and enjoyment of exercise significantly influenced both the adoption and maintenance of exercise, which underscores the need to develop regimens that maximize these factors. One important feature of the present study was the provision of a slightly lower than customary intensity of exercise. The training heart rate range was 65 to 77% of the peak value, compared to the 70% to 85% usually prescribed. This lower intensity, by 10 beats per minute, contributed to the comfort of exercise, especially among middle-aged individuals.[8,9]

The minimal staff effort and the convenience of home-based programs relying on staff telephone contact facilitate participation in monitored exercise at a relatively low cost. For example, individuals who have undergone baseline medical evaluation including exercise testing could receive 6 months of home-based exercise training using staff-initiated telephone contacts for approximately $30. This includes 30 minutes of initial instruction and 60 minutes of telephone feedback provided by staff at $20 per hour. This approach obviates the need for a group facility such as a gymnasium and thus greatly expands the availability of exercise training for healthy middle-aged individuals.

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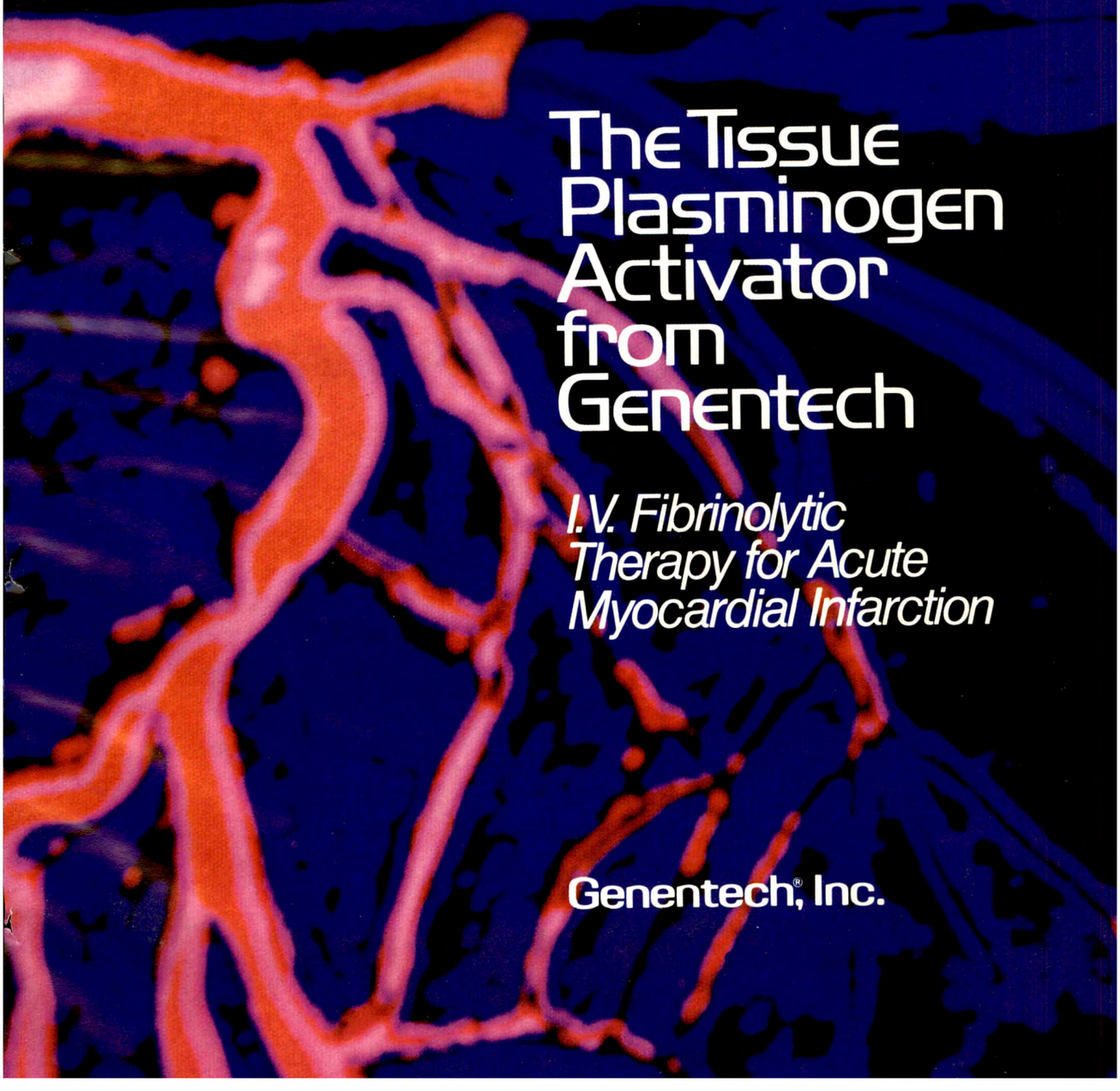

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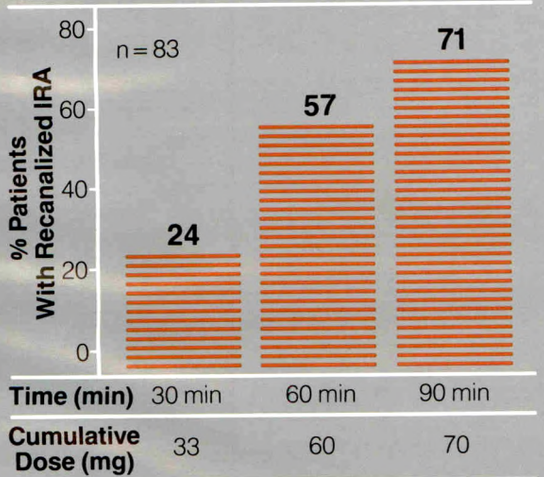

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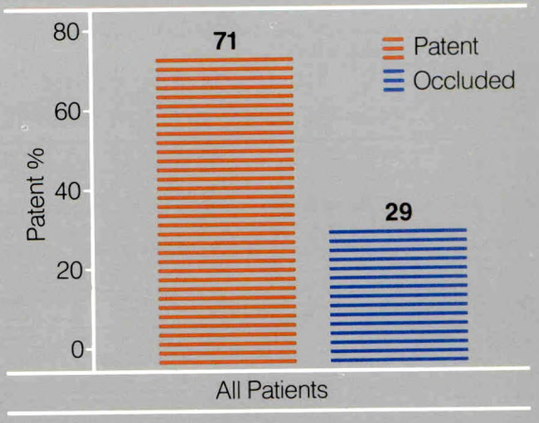

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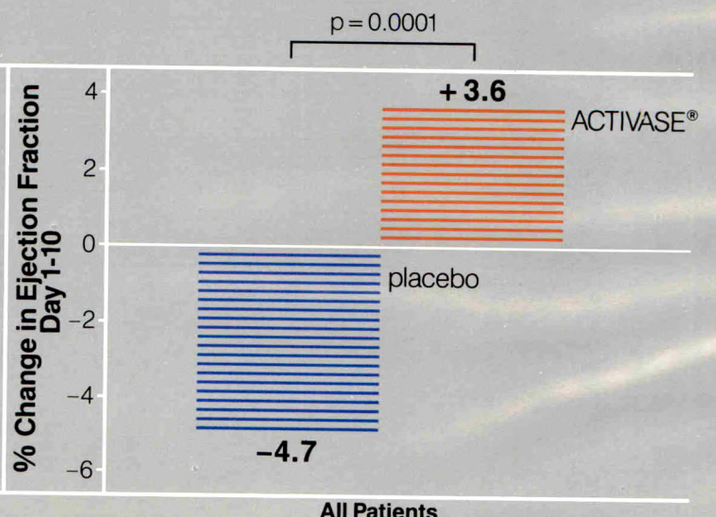

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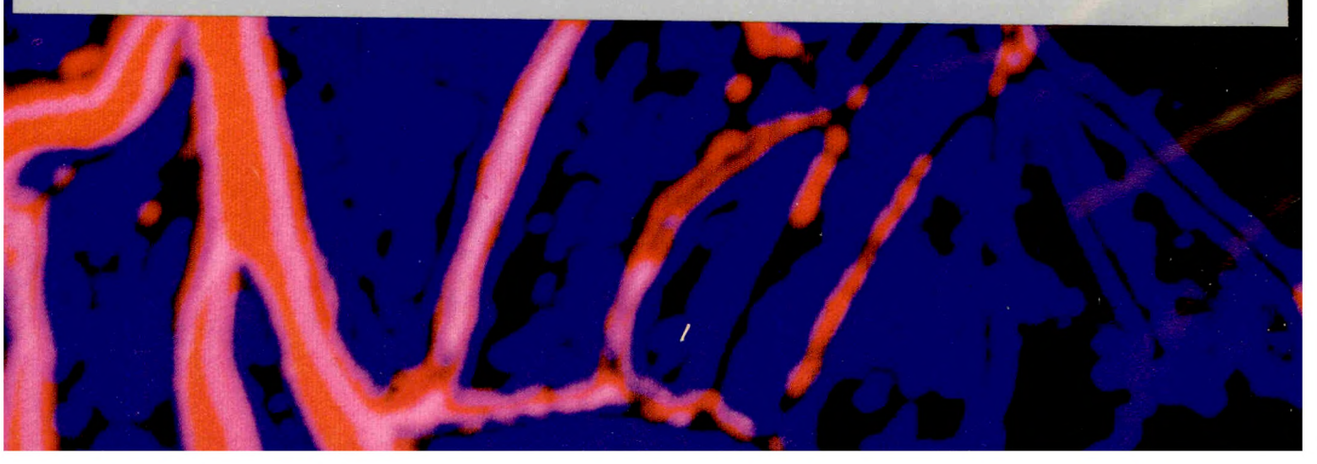

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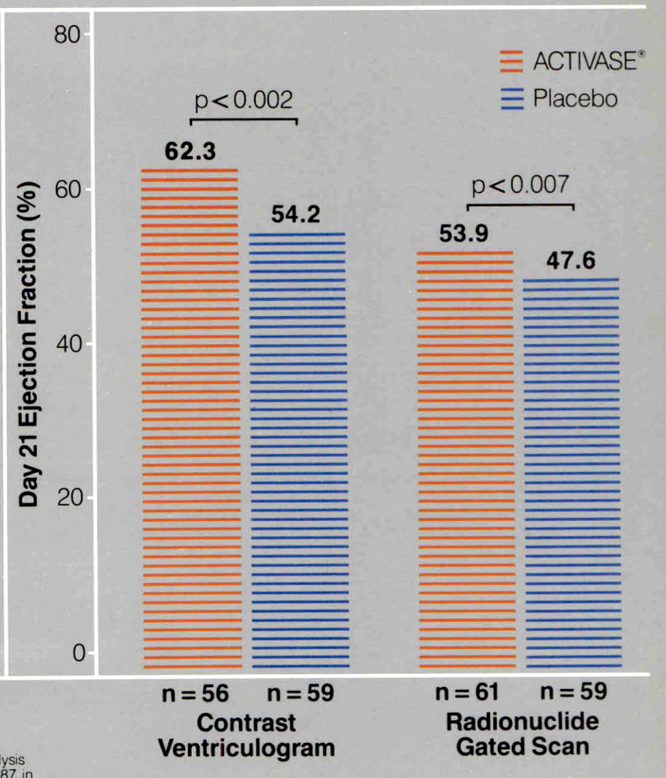
Following acute MI, and administration of ACTIVASE® or placebo, contrast ventriculogram and radionuclide gated scans were performed.

Results showed that ACTIVASE®-treated patients had significantly greater residual left ventricular ejection fractions at discharge.



4. O'Rourke M, et al. Presented at the Third International Workshop, "Thrombolysis and Interventional Therapy in Acute Myocardial Infarction," November 15, 1987, in association with the 60th Scientific Sessions of the American Heart Association, Anaheim, CA.

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ACTIVASE®
Alteplase, recombinant

I.V. fibrinolytic therapy for acute myocardial infarction

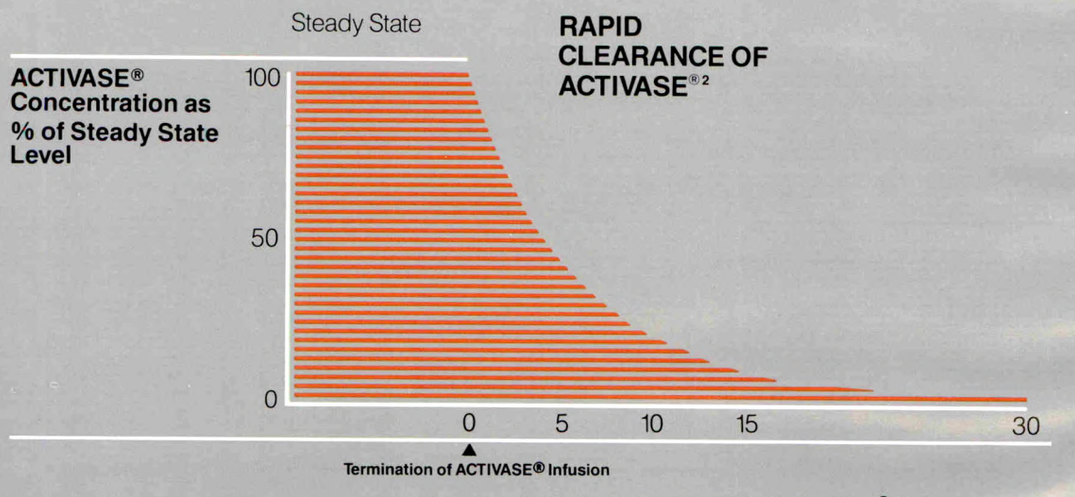
NEW

ACTIVASE®
Alteplase, recombinant

FIBRINOLYTIC SAFETY

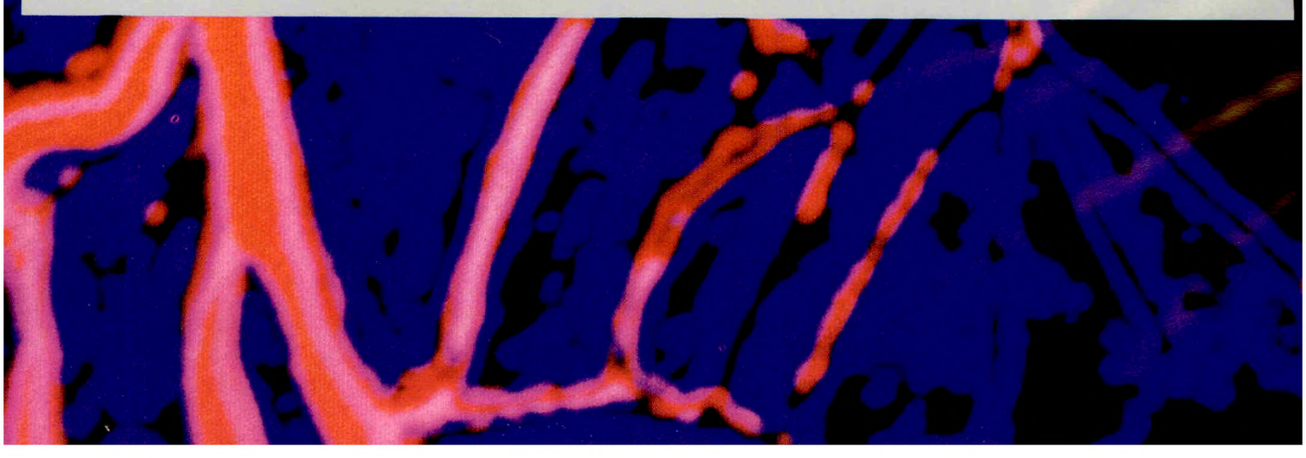
EXCELLENT SAFETY PROFILE IN ACUTE MI:

▲ FIVE-MINUTE HALF-LIFE AND FIBRIN SPECIFICITY Lower the Risk of Serious Bleeding in Emergency Procedures Such as Hemodynamic Monitoring, Angioplasty and Bypass Surgery (CABG).



▲ ACTIVASE® Is Identical to Human Tissue Plasminogen Activator (t-PA). No Serious or Life-Threatening Reactions Have Been Reported.

2. Data on file, Genentech, Inc.



In Acute Myocardial Infarction,

TIME IS MUSCLE

Bleeding is the Most Common Complication of Thrombolytic Therapy

INCIDENCE OF BLEEDING COMPLICATIONS FOLLOWING ACTIVASE® IN 848 PATIENTS:

Bleeding site	Clinically significant events %
–Arterial catheterization site	20
–Gastrointestinal (GI)	5
–Venipuncture	4
–Hematuria	4
–Occult GI	1
–Microscopic hematuria	1
–Ecchymosis	1
–Retroperitoneal	< 1
–Intracranial	0.4

Careful Patient Selection Can Optimize the Benefit-to-Risk Ratio. Consider These Factors in Evaluating an Individual for ACTIVASE® Therapy:

CONTRAINDICATIONS

–Active internal bleeding
–History of cerebrovascular accident
–Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS)
–Intracranial neoplasm, arteriovenous malformation, or aneurysm
–Known bleeding diathesis
–Severe uncontrolled hypertension

Please see ACTIVASE® (Alteplase) full prescribing information at end of this advertisement.

ACTIVASE®
Alteplase, recombinant

I.V. fibrinolytic therapy for acute myocardial infarction

NEW

ACTIVASE®
Alteplase, recombinant

In Acute Myocardial Infarction,
TIME IS MUSCLE

Rationale for ACTIVASE® Therapy

Acute MI is an evolving process caused by an occlusive coronary thrombus

I.V. administration of ACTIVASE®:

- *Opens coronary arteries rapidly, effectively, and keeps them open*
- *Improves left ventricular function, and reduces incidence of congestive heart failure*
- *Prompt intervention possible shortly after ACTIVASE® therapy due to excellent safety profile—compatible with angioplasty, bypass surgery and hemodynamic monitoring*

ACTIVASE® is a potent agent, and the benefit-to-risk ratio should be carefully considered in every patient

ACTIVASE® Dosage Schedule

Lytic dose	Bolus Hr 1	6-10mg 50-54mg
Maintenance Dose	Hr 2 Hr 3	20mg 20mg
TOTAL Recommended Dose		100mg

Available from GENENTECH

- ACTIVASE® Dosage Chart
- ACTIVASE® Product Monograph

For further information, answers to medical inquiries, and requests for literature, call the GENENTECH INFARCT LINE

1-800-821-8590

Genentech, Inc.
460 Point San Bruno Blvd.
South San Francisco, CA 94080

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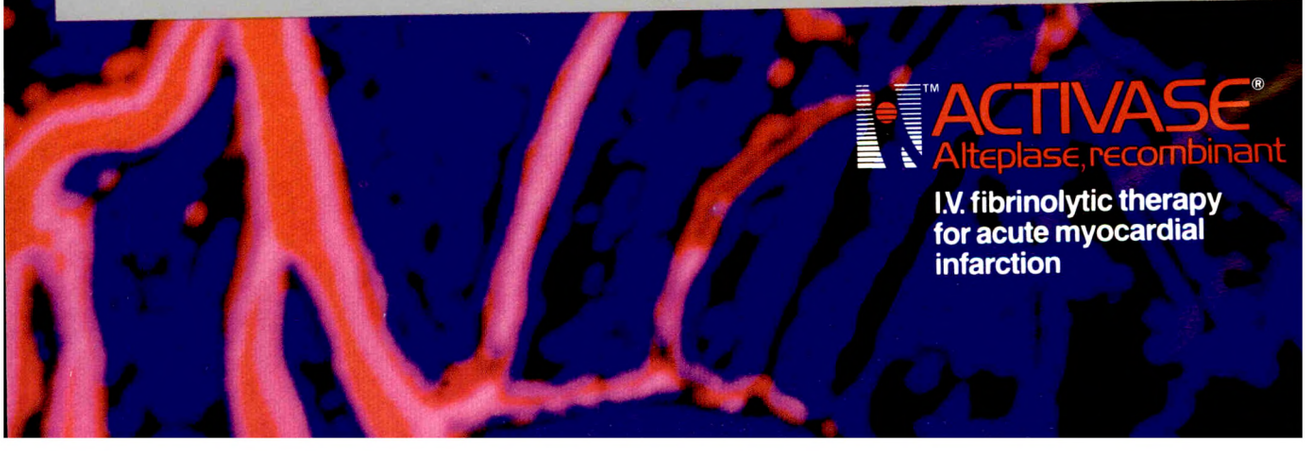

ACTIVASE®
Alteplase, recombinant
I.V. fibrinolytic therapy for acute myocardial infarction

ACTIVASE®
Alteplase, recombinant

DESCRIPTION: ACTIVASE®, Alteplase, is a tissue plasminogen activator produced by recombinant DNA technology. It is a sterile, purified glycoprotein of 527 amino acids. It is synthesized using the complementary DNA (cDNA) for natural human tissue-type plasminogen activator obtained from a human melanoma cell line. The manufacturing process involves the secretion of the enzyme, alteplase, into the culture medium by an established mammalian cell line (Chinese Hamster Ovary cells) into which the cDNA for alteplase has been genetically inserted.

ACTIVASE®, a sterile, white to off-white, lyophilized powder, is intended for intravenous administration after reconstitution with Sterile Water for Injection, USP. The quantitative composition of the lyophilized product is:

50 mg (29 million IU) Vial	20 mg (11.6 million IU) Vial
Alteplase 50 mg (29 million IU)	Alteplase 20 mg (11.6 million IU)
L-Arginine 1.7 g	L-Arginine 0.7 g
Phosphoric Acid 0.5 g	Phosphoric Acid 0.2 g
Polysorbate 80, less than 4 mg	Polysorbate 80, less than 1.6 mg

Phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment.

Biological potency is determined by an *in vitro* clot lysis assay and is expressed in International Units as tested against the WHO standard. The specific activity of ACTIVASE® is 580,000 IU/mg.

CLINICAL PHARMACOLOGY: ACTIVASE® is an enzyme (serine protease) which has the property of fibrin-enhanced conversion of plasminogen to plasmin. It produces limited conversion of plasminogen in the absence of fibrin. When introduced into the systemic circulation at pharmacologic concentration, ACTIVASE® binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis with limited systemic proteolysis. Following administration of 100 mg ACTIVASE®, there is a decrease (16-36%) in circulating fibrinogen.[1,2,3] In a controlled trial, 8 of 73 patients (11%) receiving ACTIVASE® (1.25 mg/kg body weight over 3 hours) experienced a decrease in fibrinogen to below 100 mg/dL.[2]

ACTIVASE® is cleared rapidly from circulating plasma at a rate of 550-680 mL/min. ACTIVASE® is cleared primarily by the liver. More than 50% of ACTIVASE® present in plasma is cleared within 5 minutes after the infusion has been terminated, and approximately 80% is cleared within 10 minutes.

Coronary occlusion due to a thrombus is present in the infarct-related coronary artery in approximately 80% of patients experiencing a transmural myocardial infarction evaluated within four hours of onset of symptoms.[4,5]

In patients studied in a controlled trial with coronary angiography at 90 and 120 minutes following infusion of ACTIVASE®, infarct artery patency was observed in 71% and 85% of patients (n=85), respectively.[2,3] In a second study, where patients received coronary angiography prior to and following infusion of ACTIVASE® within six hours of the onset of symptoms, reperfusion of the obstructed vessel occurred within 90 minutes after the commencement of therapy in 71% of 83 patients.[1]

In a double blind, randomized trial (138 patients) comparing ACTIVASE® to placebo, patients infused with ACTIVASE® within 4 hours of onset of symptoms experienced improved left ventricular function at day 10 compared to the placebo group, when ejection fraction was measured by gated blood pool scan (53.2% versus 46.4%, p=0.018). Relative to baseline (day 1) values, the net changes in ejection fraction were +3.6% and -4.7% for the treated and placebo group, respectively (p=0.0001). Also documented was a reduced incidence of clinical congestive heart failure in the treated group (14%) compared to the placebo group (33%) (p=0.009).[3]

In a second double blind, randomized trial (136 patients) comparing ACTIVASE®, Alteplase, to placebo, patients infused with ACTIVASE® within 2.5 hours of onset of symptoms experienced improved left ventricular function at a mean of 21 days compared to the placebo group, when ejection fraction was measured by gated blood pool scan (54% versus 48%, p=0.008) and by contrast ventriculogram (62% versus 54%, p=0.002). Although the contribution of ACTIVASE® alone is unclear, the incidence of nonischemic cardiac complications when taken as a group (i.e., congestive heart failure, pericarditis, atrial fibrillation, conduction disturbance) was reduced compared to those patients treated with placebo (p<0.01).[3]

INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the improvement of ventricular function and reduction of the incidence of congestive heart failure. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal tract, genitourinary tract, retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention).

The concomitant use of heparin anticoagulation may contribute to the bleeding. Some of the hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE®. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE®, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE®, Alteplase, and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent gastrointestinal or genitourinary bleeding (within 10 days) • Recent trauma (within 10 days) • Hypertension: systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants, e.g., warfarin sodium • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE® are administered.

PRECAUTIONS: General Standard management of myocardial infarction should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided (i.e., internal jugular and subclavian punctures should be avoided to minimize bleeding from noncompressible sites). Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE®. If an anaphylactoid reaction occurs, the infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution. Detectable levels of antibody (a single point measurement) were reported in one patient but subsequent antibody test results were negative.

Laboratory Tests During ACTIVASE® therapy, if coagulation tests and/or measures of fibrinolytic activity are performed, the results may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In

addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole) may increase the risk of bleeding if administered prior to, during or after ACTIVASE® Alteplase, therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE®. It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding, involving the gastrointestinal tract, genitourinary tract, retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention).

The following incidence of significant internal bleeding (estimated as > 250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	< 1%
retroperitoneal	< 1%	< 1%
epistaxis	< 1%	< 1%
gingival	< 1%	< 1%

The incidence of intracranial bleeding (ICB) in patients treated with ACTIVASE® is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Although fatalities due to intracranial bleeding have been observed during and after ACTIVASE® therapy, an analysis of data from three controlled clinical trials in acute myocardial infarction revealed no evidence of increased overall in-hospital mortality. While not statistically significant, in-hospital mortality in patients treated with ACTIVASE® Alteplase, was lower (4.7%, 11/232) compared to patients not receiving ACTIVASE® (6.8%, 11/162).[3]

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin which is part of the hemostatic plug formed at needle puncture sites will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites, e.g., catheter insertion sites, arterial puncture sites.

Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of myocardial infarction and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: Administer ACTIVASE® as soon as possible after the onset of symptoms.

Lysis of coronary artery thrombi has been documented in 71% of patients treated with ACTIVASE® within 6 hours of onset of symptoms.[1] Improvement of ventricular function and reduction of the incidence of congestive heart failure have been documented in patients treated within 4 hours of the onset of symptoms.[3]

ACTIVASE® is intended for administration by intravenous infusion only.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.[5]

A DOSE OF 150 MG OF ACTIVASE, ALTEPLASE, SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 48 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Reconstitution should be carried out using a large bore needle (e.g., 18 gauge), directing the stream of Sterile Water for Injection, USP into the lyophilized cake. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for direct intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE® Alteplase, may be administered as reconstituted at 1.0 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass bottles are acceptable. ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE®. Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum.

Each 20 mg ACTIVASE® vial (11.6 million IU) is packaged with diluent for reconstitution. (20 mL Sterile Water for Injection, USP): NDC 50242-044-12.

Each 50 mg ACTIVASE® vial (29.0 million IU) is packaged with diluent for reconstitution. (50 mL Sterile Water for Injection, USP): NDC 50242-044-13.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

ACTIVASE® Alteplase, recombinant
Manufactured by
GENENTECH, INC.
460 Point San Bruno Boulevard
South San Francisco, CA 94080
November, 1987

REFERENCES: 1. Mueller H, Rao AK, Forman SA, et al: Thrombolysis in myocardial infarction (TIMI): Comparative studies of coronary reperfusion and systemic fibrinogenolysis with two forms of recombinant tissue-type plasminogen activator. *J Am Coll Cardiol* 1987; 10:479-490. **2.** Topol EJ, Morriss DC, Smalling RW, et al: A multicenter, randomized, placebo-controlled trial of a new form of intravenous recombinant tissue-type plasminogen activator (ACTIVASE®) in acute myocardial infarction. *J Am Coll Cardiol* 1987; 9:1205-1213. **3.** Unpublished data, Genentech, Inc. **4.** De Wood MA, Spores J, Notske R, et al: Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *New Engl J Med* 1980; 303:897-902. **5.** Chesebro JH, Knatterud G, Roberts R, et al: Thrombolysis in myocardial infarction (TIMI) trial, phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. *Circulation* 1987; 76(1): 142-154. **6.** Califf RM, Stump D, Thornton D, et al: Hemorrhagic complications after tissue plasminogen activator (t-PA) therapy for acute myocardial infarction. *Circulation* 1987; 76:IV-1.

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Optimum Heart Rate of Large Failing Hearts

HERBERT J. LEVINE, MD

". . . like warp and woof, mechanism and teleology are interwoven together, and we must not cleave to one nor despise the other for their union is rooted in the very nature of totality."

Sir D'Arcy Wentworth Thompson

Big hearts beat more slowly than small hearts. While this observation seems patent and even borders on tautology, the reasons for it may not be quite so obvious. The inherent frequency of a large machine will be slower than that of a similar small machine. It boggles the mind to imagine an elephant heart with atrial fibrillation beating at a rate of 180 beats/min, yet it does not surprise us that a human heart weighing 300 g might do so. Little consideration has been given in clinical medicine to adjusting heart rate (HR) to heart size. What is the intrinsic frequency of an 800-g heart in a patient with systemic hypertension, hypertrophic cardiomyopathy or idiopathic dilated cardiomyopathy? Should the optimal HR for pacemaker-dependent patients be normalized for heart size? Should we not expect a slower HR in patients with aortic stenosis or systemic hypertension than in those with mild mitral valve disease?

To answer these questions, one might begin with an allometric analysis of relevant biologic parameters among animals of different size. Examining the relation between resting HR and body mass among mammals spanning a body weight from 3,000 kg (elephant) to 3 g (shrew), a linear relation between logarithmic coordinates is observed.[1] Furthermore, because heart weight is nearly proportional to body weight (comprising 0.6% of body weight in small and large mammals alike), an inverse relation between heart weight and HR can be established. In addition, the regression line on logarithmic coordinates between body mass and resting oxygen consumption among mammals has exactly the same slope as that between body mass and HR.[1] Thus, from these data it may be concluded that the HR increase in smaller mammals is in exact proportion to the increase in metabolic rate. Such increases are the consequence of a biophysical imperative. Since heat production will depend on the mass (the cube of a linear dimension) and heat loss through the surface of an organism as the square of a linear dimension, as an animal becomes smaller, the ratio of surface area to mass increases and the relative heat loss will increase, necessitating a rise in metabolic rate to provide the same quantity of usable energy. Thus, while human beings consume 1 to 2% of their body weight in food per day, a mouse will devour 50% of its body weight daily.

On the basis of these observations, it is reasonable to conclude that the slower HRs in larger mammals are the consequence of a lower metabolic rate. However, if the inverse relation between intrinsic HR and heart size is valid for humans with varying degrees of cardiomegaly, a different explanation must be sought, since a number of studies have shown that resting unit myocardial oxygen consumption in patients with large failing hearts is normal despite heart weights which may be as much as 3 times heavier than normal.[2,3] Thus, a slower HR in large human hearts cannot be attributed to a lower myocardial metabolic rate. There is reason to believe that other factors may determine the intrinsic frequency of hearts of varying size. Birds have bigger hearts and slower HRs than mammals of equal size. In addition, their cardiac output is higher for a given metabolic rate and the allometric relation between oxygen consumption and body mass predicts that a 1-kg bird will have a higher oxygen consumption than a 1-kg mammal.[4] According to Grubb,[4] the HR of a 1-kg bird will be 178 beats/min whereas that of a comparable sized mammal will be 236 beats/min. It would appear, therefore, that the slower HR in birds compared with mammals is not related to metabolic rate and may be a consequence of the larger heart size itself.

Support for this possibility may be found in Froude's law of the correspondence of speeds. This law states that speed varies as the square root of the linear dimension. As illustrated by Sir D'Arcy Thompson, this principle has provided an accurate basis for comparing the maximum speed of fish, ships or birds in flight and in relating a variety of other biologic phe-

From the Department of Medicine, Tufts University School of Medicine and New England Medical Center, Boston, Massachusetts. Manuscript received August 3, 1987; revised manuscript received and accepted October 28.

Address for reprints: Herbert J. Levine, MD, Cardiology Division, New England Medical Center, Boston, Massachusetts 02111.

nomena.[5] More relevant to the question of the HR of hearts of differing size, is the application of Froude's law which dictates that, among similar pendulums, the time of the swing varies as the square root of the pendulum length.[5] If we were to apply this principle to the comparison of the intrinsic HR of a normal and enlarged heart (volume 3 times larger than normal) and assume the heart rate of the normal heart to be 75 beats/min, the linear dimension of the larger heart would be 1.44 times bigger than normal and the intrinsic heart rate 62 beats/min.

Hill, however, suggested that among animals the relation between speed and length is linear[6] and that allometric velocity characteristics are determined more by differences in metabolic rate than by Froude's law. In bird flight, wing-beat frequency is approximately inversely proportional to the linear dimension of the bird.[5] If such is the case, the intrinsic HR of the large heart described above would be 52 instead of 62 beats/min. Whether this approach is appropriate for humans is unknown and, unfortunately, allometric data of this sort derived from human studies is sparse. Harrison et al[7] examined the relation between myocardial fiber thickness and heart rate among normal human hearts from infancy to adulthood and provided some helpful information. As shown in Figure 1, the relation between myocardial fiber thickness and HR among normal infants, children and adults appears to be exponential. However, the HRs of large, nonfailing and failing hearts were considerably faster than those we would have predicted from the semi-logarithmic relation derived from normal hearts. Thus, the HRs of these large nonfailing and failing hearts were observed to be 84 and 76 beats/min, whereas extrapolation of the data obtained from the normal hearts would predict these values to be 33 and 8 beats/min, respectively. Because the data from normal hearts were derived from humans with marked variations in body

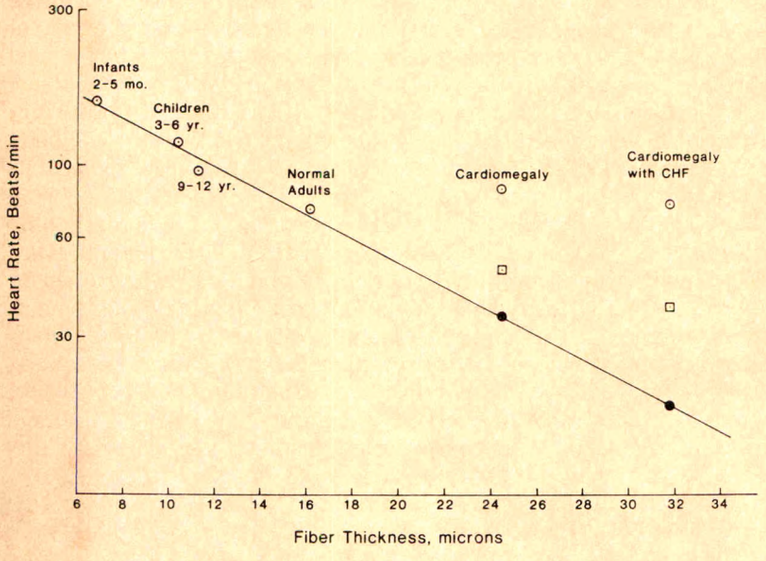

FIGURE 1. Relation between heart rate and myocardial fiber thickness. Values for normal infants, children and adults, and adult patients with large, nonfailing and failing hearts are indicated by the *open circles* (data from Harrison et al).[7] The *solid circles* indicate the heart rate predicted for patients with cardiomegaly (with and without congestive heart failure), extrapolated from the data obtained from normal hearts. The *open squares* indicate the heart rate calculated by assuming an inverse linear relation between fiber thickness and heart rate (see text). CHF = congestive heart failure.

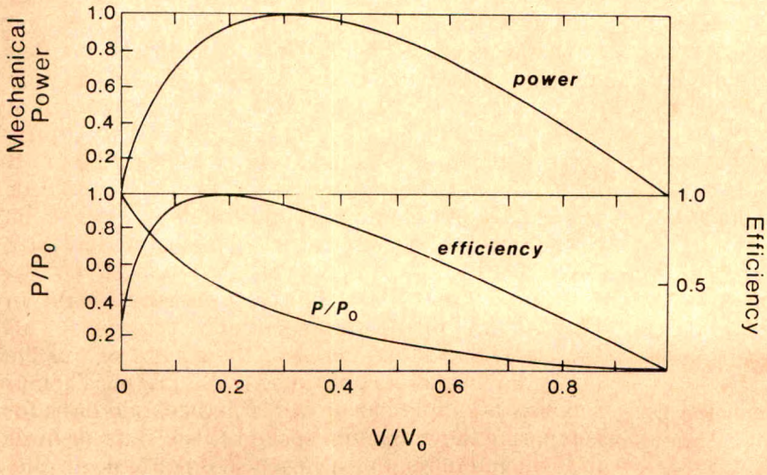

FIGURE 2. Relation between various mechanical properties of muscle and speed of shortening. Speed (V) as fraction of maximum speed (V_0) under zero load. Force (P) as fraction of maximum force (P_0) at zero speed. Efficiency equals mechanical work done divided by total energy used. Mechanical power equals the product of force and speed (PV). From experiments on isolated muscles and on man. Adapted from Hill.[6]

size, the metabolic rate was not constant and thus the allometric analysis of HR rate must be adjusted accordingly. The real question to be solved is the reaction between HR and heart size when the myocardial metabolic rate remains constant. Assuming, as Hill suggests, that the inverse relation between frequency and linear dimension of heart muscle (fiber thickness) is linear rather than exponential, the predicted HR in these 2 groups of large hearts would be 48 and 37 beats/min (Figure 1).

Whether these allometric comparisons should employ linear or exponential functions is problematical. What is clear, is that given their druthers, large hearts would rather beat more slowly than normal sized hearts. The impact of this conclusion becomes greater when we consider that a general response of the failing heart is an increase in HR. Whereas this might not be of concern during the acute phase of heart failure, as cardiac dilatation and hypertrophy evolve, the increase in HR may not be entirely self-serving. The HR response is an effective mechanism for compensating for reduced contractile performance and reduced stroke volume. Indeed, the enhanced neurohumoral activity of the sympathetic nervous system in congestive heart failure provides the mechanism for this adaptation. Yet, although there are HR-increasing forces at play in hypertrophy and failure, other changes may move velocity indexes in the opposite direction. In some species during pressure-overload hypertrophy and with aging, the myosin isoenzyme composition shifts to the predominant V_3 form with its characteristic reduced ATPase activity.[8] Among mammals of differing size, Barany[9] has shown a close correlation between myosin ATPase activity and the inherent speed of muscle shortening. Reduced myosin ATPase activity is also evident in the sluggish hearts of humans with congestive heart failure.[10]

For hearts of any size there appears to be an optimum frequency at which the power and efficiency of contraction are near maximum. Although the specific relation between these variables may not be known, analogous data regarding the mechanical properties of muscle and the speed of shortening should provide a comparable model. In Figure 2, adapted from Hill,[6] the relation between load and velocity of shortening and the mechanical power and efficiency of muscle is shown. Maximal power and efficiency are achieved at approximately 0.2 to 0.3 times the maximal velocity, and at velocities above and below this level, power and efficiency fall off sharply. Whether the malefic effect of tachycardia in large hearts is due more to prolonged diffusion through thicker myocardial fibers, as suggested by Harrison et al,[7] or to inherent mechanical characteristics of large muscles is unknown. Regardless, it is clear that mismatch between HR and cardiac performance may have the same implications as does afterload mismatch in failing myopathic ventricles. The modern approach in treating congestive heart failure exploits afterload mismatch by interrupting compensatory systemic vascular constriction. Indeed, the success of this intervention may be due in part to the steep portion of the efficiency-load curve at high values of P/P_0 shown in Figure 2. In this circumstance, a reduction in afterload (P/P_0) would be expected to evoke a substantial increase in total power and efficiency of cardiac contraction. While the shape of the curve relating the optimal HR to the performance of large failing hearts is not known, the principle appears sound and is worthy of investigation.

The reports from Göteborg in 1975 of a beneficial effect of β-adrenergic blockade in patients with dilated cardiomyopathy[11] surprised cardiologists and were initially greeted with skepticism. After a decade of cautious experimentation, most investigators today believe that there are many patients with dilated cardiomyopathy who have improved ventricular performance and clinical status with this form of therapy. Although many explanations have been suggested, cardiac slowing is a constant feature of this therapy and quite possibly may be the change responsible for the benefit observed. With the availability of new specific bradycardiac agents relatively devoid of negative inotropism, hypotension and membrane effects,[12] the opportunity is at hand to test this hypothesis in clinical trials.

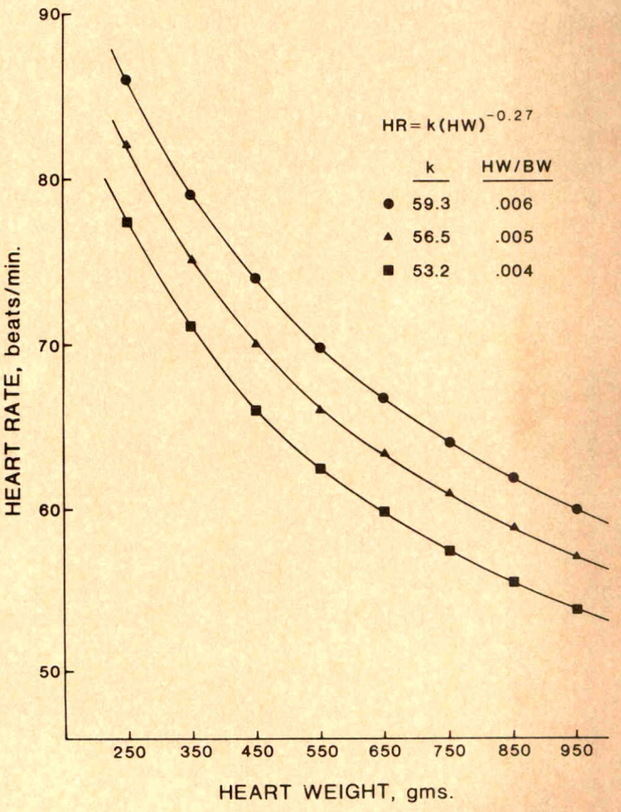

FIGURE 3. Relation between heart rate and heart weight. Adapted from Clark,[13] who suggests that heart rate varies in inverse proportion to the 0.27 power of body weight. The constants (k) assume the resting heart rate of a 70-kg man is 75 beats/min for heart weight/body weight ratios of 0.006 (●), 0.005 (▲) and 0.004 (■). BW = body weight; HR = heart rate; HW = heart weight; k = constant.

Perhaps the first step in examining the effects of heart size on the optimal HR would be to develop an algorithm applicable to clinical practice. Were it possible to accurately assess heart mass in cardiac patients, estimates of the inverse relation between HR and heart size could be derived by application of the principle of similitude in biology. Clark[13] has suggested that HR varies in inverse proportion to the 0.27 power of body weight. With this as a starting point, a rough approximation may be made of the variation in intrinsic HR expected to correspond to a range of heart size encountered in clinical medicine. The data presented in Figure 3 has been calculated by adapting the Clark formula to relate HR to heart weight. Using the constant derived from a heart weight/body weight ratio of 0.005, doubling a normal heart weight of 300 g would slow HR from 78 to 65 beats/min and a 3-fold increase in heart weight would predict an optimal HR of 58 beats/min. The patients with dilated cardiomyopathy reported by Waagstein et al[11] who benefited from β-adrenergic blockade had a mean fall in HR from 98 to 69 beats/min. These data provide only a crude estimate of the inverse relation between HR and heart size, but there is reason to believe that the expected values for the HR of large hearts are acceptable and in keeping with a number of biophysical predictions.

It would appear, that not only is there an optimal match between preload and the diastolic properties of the ventricle and between afterload and ventricular systolic function, but also between HR and the size and mechanical characteristics of the heart. Indeed, the interrelation between HR mismatch and both preload and afterload mismatch are obvious. In hypertrophic cardiomyopathy, prolongation of diastole alone will reduce elevated ventricular filling pressures and help compensate for delayed relaxation and reduced ventricular compliance. It is likely that the proper HR for optimal systolic function will not always be the same as that for optimal diastolic function, and the utility of bradycardiac therapy in patients with large hearts will need to be determined by trial. It is clear that the optimal HR must conform to nature's scale, and the warp and woof of this fabric is the relation of HR to cardiac mass.

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Usefulness of Aspirin for Coronary Artery Disease

VALENTIN FUSTER, MD, MARC COHEN, MD, and JAMES H. CHESEBRO, MD

Aspirin was first synthesized in 1859. Because of its antipyretic and analgesic effects, relatively good tolerance, low cost and easy accessibility, aspirin continues to be the most consumed drug today. In the U.S. alone, between 20 and 30 billion tablets are ingested each year. Surprisingly, for such an old and often used drug, therapeutic discoveries are still being made. Further, aspirin's role in our number 1 public health problem, coronary artery disease, is still evolving.

In the late 1960s, aspirin, was discovered to have antiplatelet effects.[1] Its role in the prevention of coronary platelet thrombosis, then considered to be the cause of heart attacks, began to be anticipated. During the 1970s such hopes dissipated. First, the role of thrombosis in acute myocardial infarction was questioned. Second, a number of major drug trials of aspirin prophylaxis in survivors of myocardial infarction showed only a minor beneficial trend in the prevention of recurrent coronary events.

In the 1980s, a renewed interest in platelets and thrombosis, and consequently aspirin, has emerged especially in relation to acute coronary syndromes such as unstable angina and reocclusion after thrombolysis for acute myocardial infarction.[2-6] First, recent research has identified a definitive role for thrombosis in the pathogenesis of some acute coronary syndromes. Second, based on a better understanding of the natural history of coronary artery disease, drug trials of aspirin have been more properly designed allowing the benefits of the drug to become more apparent. Third, advances in the pharmacologic effects of aspirin are guiding investigators to search for the lowest dose of the drug with maximal anithrombotic effect and minimal risk of bleeding. Lastly, recent insights into platelet physiology indicate that aspirin alone may not be equally effective in all clinical settings involving platelet aggregation and thrombosis.

From the Division of Cardiology, Department of Medicine, the Mount Sinai School of Medicine of the City University of New York, New York, and Mayo Clinic, Rochester, Minnesota. Manuscript received July 14, 1987; revised manuscript received and accepted October 21, 1987.

Address for reprints: Valentin Fuster, MD, Division of Cardiology, Box 1030, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, New York 10029.

Role of Platelets and Thrombosis in the Acute Coronary Syndromes

Pathoanatomic studies: Pathoanatomic studies with meticulous histologic sectioning of the coronary arteries, including 100 to 1,000 sections of each segment with complicating thrombosis, have revealed that rupture, fissuring or ulceration of atherosclerotic plaques is a common autopsy finding in patients with coronary atherosclerotic disease experiencing fatal myocardial infarction or sudden death.[2-6] Over three-quarters of the ruptured atherosclerotic plaques have associated mural or occlusive thrombi.[2-6] Most important, most coronary artery thrombi have platelets at the base and are anchored in the cracks or ruptured atherosclertoic plaques.[2-7] Recent clinical investigations of acute coronary syndromes, applying different techniques, have confirmed this relation found at autopsy between plaque rupture and thrombosis; the techniques used were serial coronary arteriography,[8] retrieval of thrombi at operation during acute coronary artery syndromes,[9] reperfusion by thrombolysis,[10] angiographic morphology of ischemia-producing lesions both in vivo and using barium casts of the coronaries at postmortem[11,12] and intraoperative angioscopy.[7] Thus similar "anatomic accidents," consisting of plaque rupture and superimposed thrombosis, appear to be the most frequent cause of the acute coronary syndromes, including unstable angina, myocardial infarction and sudden coronary death.[13]

Physiologic studies: Physiologic studies have identified 5 important factors in the genesis of thrombi that complicate a ruptured atherosclerotic plaque.[13,14] They are (1) fibrillar collagen exposed to the flowing blood activates platelets and the intrinsic clotting cascade; (2) thromboplastin released from the damaged vessel activates the extrinsic clotting cascade forming thrombin, which leads not only to fibrin formation but also platelet aggregation; (3) hemorrhage into the plaque leads to release of adenosine diphosphate from erythocytes, which further amplifies platelet aggregation; (4) fatty gruel underneath the plaque is exposed to blood and activates platelets; and (5) luminal stenosis

by the plaque predisposes to turbulent blood flow, increased wall shear stress or stasis, all of which may promote platelet aggregation and thrombosis.

Clinical Trials of Aspirin

Secondary prevention trials: With the objective of preventing coronary thrombosis, 6 major controlled trials of aspirin prophylaxis in survivors of myocardial infarction were conducted in the 1970s. The trials showed a consistent trend toward a reduced incidence of recurrent myocardial infarction and death, but none achieved statistical significance.[15–20] Three main possibilities may explain the lack of a more striking beneficial effect. First, sample size may have been inadequate in view of the relatively low rate of reinfarction, a low *sensitivity* endpoint after transmural acute myocardial infarction. Second, the studies were done soon after myocardial infarction when early sudden death is known to be more closely related to irreversible ventricular dysfunction,[21] rather than to a preventable coronary thrombotic process that could potentially be prevented by aspirin. That is, a low *specificity* endpoint may also partly explain the lack of striking benefit in the aspirin-treated groups. In this context, a trial of anticoagulants versus placebo in patients more than 60 years old who had their previous myocardial infarction a median of 6 years before showed about a 50% reduction over 2 years in recurrent myocardial infarction and total mortality in the treated group.[22] The greater benefit shown in this study compared with the previous studies may be partly explained on the grounds that this was a stable group of patients in whom coronary thrombosis, potentially preventable by antithrombotic therapy rather than myocardial dysfunction, may have dictated the long-term prognosis.

The third possibility that may explain the lack of a more striking beneficial effect of aspirin may be related to a heterogeneity of mechanisms leading to rethrombosis in patients who have experienced a myocardial infarction. Aspirin only blocks platelet aggregation resulting from the activation of the prostaglandin system. It does not block platelet aggregation and fibrin formation resulting from other mechanisms, for example, adenosine diphosphate or the generation of thrombin.

Unstable angina and bypass graft patency trials: In contrast to the population recruited in the secondary prevention trials, patients with unstable angina do have a higher event rate for myocardial infarction and ischemic sudden death, and such events are most likely specifically thrombotic. In fact, 2 major, multicenter, double-blind, placebo-controlled trials of aspirin therapy in patients with unstable angina have been conducted and both showed a significant beneficial effect of therapy. In the Veterans Administration Cooperative Study[23] aspirin treatment (324 mg in buffered solution daily) for 12 weeks was tested in 1,266 men with unstable angina. The incidence of acute myocardial infarction or death was 51% lower in the aspirin-treated group (5%), compared with the placebo group (10%). The Canadian Multicenter Trial[24] used a higher dose of aspirin (325 mg 4 times daily) and observed their patients over a mean follow-up period of 18 months. The incidence of either nonfatal acute myocardial infarction or death was also 51% lower for patients treated with aspirin (9%), compared with those not given aspirin (17%).

Another area where platelet deposition and mural thrombus formation clearly play a crucial role is the occlusion of aortocoronary artery vein grafts. Chesebro et al[25] have demonstrated that therapy with dipyridamole, started 2 days before surgery and given on the morning of the operation and 1 hour after the procedure, plus aspirin (325 mg 3 times daily) added 7 hours after the operation, is highly effective in improving early postoperative vein graft patency. Moreover, this combined treatment appears to be of continued benefit 1 year after the operation.[26] More recent studies by Lorenz,[27] Goldman[28] and their co-workers have shown that a daily dose of only 100 mg or 325 mg of aspirin, respectively, significantly reduced aortocoronary bypass vein graft occlusion. Based on these recent aspirin trials in patients with coronary disease, the potential benefits of aspirin, even at a low dose, are beginning to emerge.

Primary Prevention Trials

Preliminary results from a double-blinded controlled trial in 22,000 male U.S. physicians assigned to receive buffered aspirin (325 mg every other day) or placebo for 5 years revealed a significant reduction in myocardial infarction from approximately 0.4% to 0.2% per year.[29] In advising the wide use of aspirin for primary prevention to apparently normal people there are 3 concerns: (1) the incidence of hemorrhagic stroke was slightly increased in the aspirin group; (2) a randomized primary prevention British study that involved 5,000 doctors taking aspirin 500 mg daily or placebo found no significant reduction in myocardial infarction but an increase in disabling stroke[30]; and (3) the very long-term effects of aspirin in blocking the prostaglandin metabolic pathway in various tissues (i.e., central nervous system) is unknown. Therefore, in our view aspirin should only be advised for primary prevention to individuals at very high risk for coronary disease, perhaps with the exclusion of hypertension because of increased risk of hemorrhagic stroke.

Ideal Dose of Aspirin

Primary inhibitors of the cyclooxygenase enzyme, such as aspirin, when given in a large dose, might inhibit not only platelet production of thromboxane A_2 and thereby platelet activation and aggregation, but also vessel wall synthesis of prostacyclin, an inhibitor of platelet aggregation.[31] Therefore, concerns have been raised regarding the possibility of attenuation of the platelet inhibitory effect by high aspirin dosage, or even its potential thrombogenicity. Such concerns have been overestimated. Epidemiologic studies of patients with rheumatoid arthritis treated with a very large dose of aspirin have not demonstrated an increase in thrombosis or atherosclerosis; this suggests that even high doses of aspirin are not thrombogenic in man.[32]

While high dose aspirin therapy may not enhance thrombogenicity, it is becoming more apparent that lower dose aspirin may be sufficient to achieve the desired antithrombotic benefit without significant side effects (gastrointestinal manifestations). Experimental demonstration that low dose (<1.0 mg/kg daily) aspirin was a selective and adequate inhibitor of thromboxane A_2-related platelet function[33] was quickly corroborated by observing clinical benefit from low dose regimens. As already noted, beneficial results were obtained with use of a relatively low dose of aspirin by the Veterans Administration study on unstable angina,[23] the Veterans Administration study on bypass graft patency[28] and the study of Lorenz et al.[27] Further, a recent clinical trial has shown clinical benefit (reduction in the incidence of hypertension and preeclampsia), with aspirin doses of 60 mg daily.[34]

All of these studies favoring low dose aspirin are important because if antithrombotic effects can be achieved with a minimal dose of the drug, the toxic side effects associated with higher dosages will be avoided. The side effects of aspirin are mainly gastrointestinal and dose related. Based on several trials using aspirin (900 mg daily or greater) in coronary artery disease,[15-20,24] the main side effects were stomach pain, heart burn, nausea and constipation, occult gastrointestinal blood loss and in a small percentage of patients, hematemesis and melena. In contrast, with low dose aspirin versus placebo, the Veterans Administration Cooperative Study on unstable angina[23] (aspirin 324 mg daily) showed "no significant differences in the incidence of epigastric burning or discomfort, decreased hemoglobin concentration, or occult blood in the stool."

It may also be argued that very low dose aspirin (<1 mg/kg) is preferable because previous studies suggested that lower doses may not inhibit vascular synthesis of prostacyclin.[33] The clinical relevance of selective inhibition of platelet cyclooxygenase, however, is doubtful. A recent study assessing local synthesis of prostacyclin after vessel injury failed to observe selective inhibition of platelet versus endothelial cyclooxygenase after 35 mg daily of aspirin.[35] Further, vessel walls diseased by atherosclerosis (the usual site of acute thrombotic activity) may not have normal endothelial surfaces that are capable of synthesizing prostacyclin. Finally, if very low doses of aspirin are used in the future, studies need to be done that prove that they are adequately absorbed by 100% of the patient population.

Based on these observations, we recommend 325 mg as the current therapeutic dose for aspirin. Doses between 60 and 325 mg will possibly be recommended in the near future based on clinical trials currently underway. Lastly, trials also need to be done to assess the clinical efficacy of aspirin doses <60 mg.

Platelet Physiology and Implications for Future Trials

Aspirin irreversibly acetylates the enzyme cyclooxygenase, thereby inhibiting thromboxane A_2 synthesis. Thromboxane A_2 activates the surface membrane of nearby platelets increasing their intracytoplasmic calcium and promoting more platelet aggregation. Besides being a potent inducer of irreversible platelet aggregation, thromboxane A_2 also constricts vascular smooth muscle. Thus, the beneficial effects of aspirin in unstable angina might be theoretically related to prevention of platelet aggregation and subsequent vascular occlusion, to prevention of vasopasm or to both. However, there may be other triggers leading to thrombotic-related myocardial infarction or death. In fact, aspirin-exposed platelets can still display a full aggregatory reaction in response to stimuli such as fibrillar collagen, adenosine diphosphate or thrombin, despite total suppression of thromboxane A_2 synthesis. Further, surface interactions between platelets and vessel wall, von Willebrands factor and fibrinogen may take place independently of thromboxane A_2.[36] Failure to fully appreciate such heterogeneity of mechanisms leading to platelet aggregation and thrombosis and aspirin's limited point of attack can lead to overestimating its therapeutic potential. Indeed, in the Veterans Administration Cooperative Study[23] and the Canadian Multicenter Trial[24] on unstable angina, the rate of transmural infarction or death was 5 and 9%, respectively. What remains to be established is whether the use of a more aggressive antithrombotic regimen, such as combination therapy with aspirin plus an anticoagulant, may result in an even lower morbidity, mortality and medical failure rate.

Therapy with aspirin plus an anticoagulant has been used in 3 previous trials in patients with prosthetic heart valves.[37-39] Two trials showed that combination therapy was more efficacious in reducing thromboembolism.[38,39] Combination therapy has also been tested in recent experimental work in the pig model using carotid artery injury induced by balloon angioplasty.[40] In this model, heparin (1 mg/kg daily) was effective in reducing thrombus formation, but the combination of aspirin plus heparin was substantially more effective.

It might be anticipated that the combination of aspirin with anticoagulants would produce more adverse effects than either drug alone. In fact, studies using ≥0.5 g of aspirin a day in combination with warfarin anticoagulation resulted in an excess of gastrointestinal bleeding complications.[39] It is possible, however, that the use of low dose aspirin (≤60 mg), which would be less likely to cause local gastric irritation, may be safely combined with warfarin therapy. The potential impact of a safe combination regimen in patients with coronary artery disease should be determined in future clinical trials.

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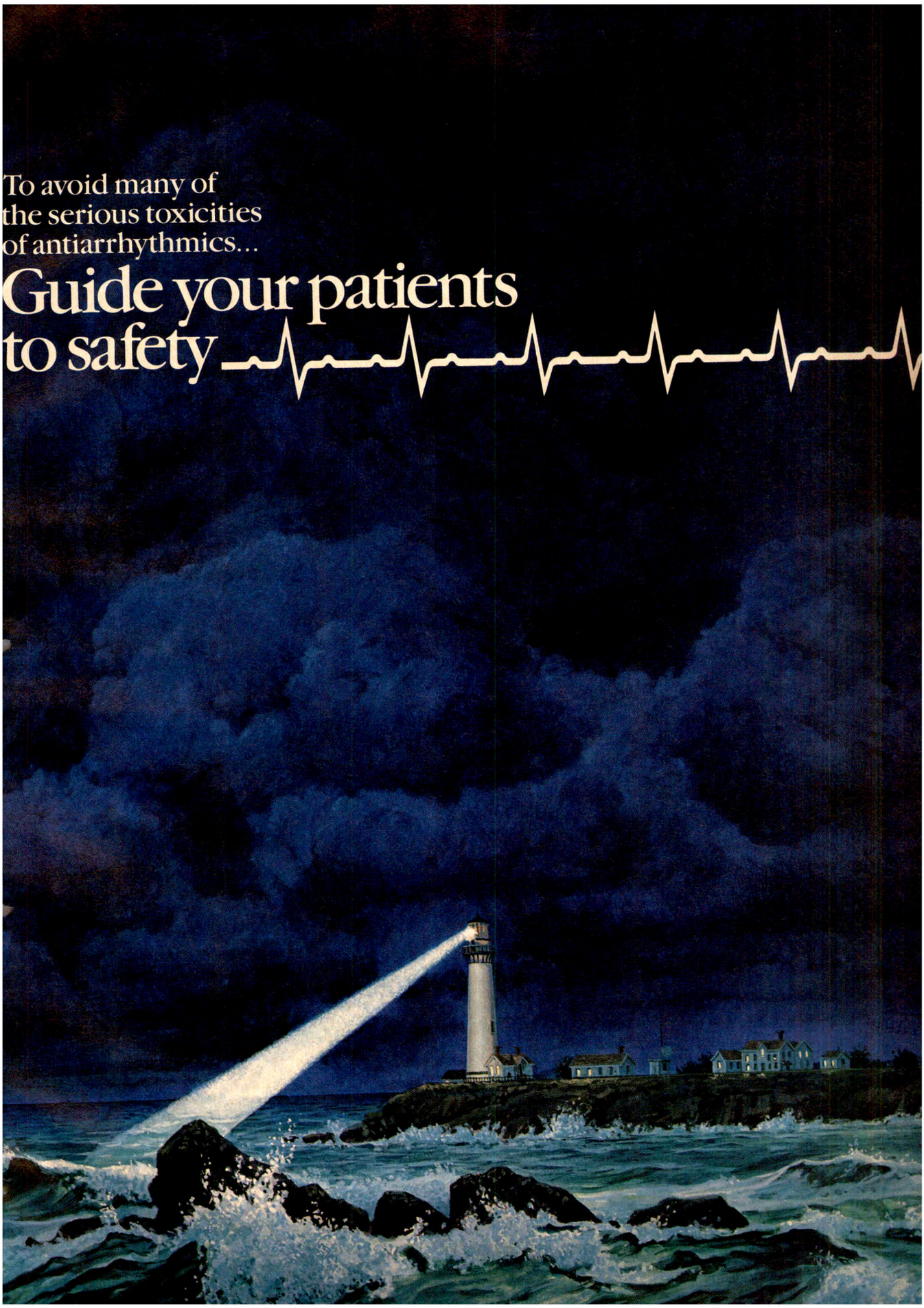
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MEXITIL is as effective as quinidine, procainamide, disopyramide, and tocainide in controlling ventricular arrhythmias including PVCs, couplets, and V Tach.[1-6]

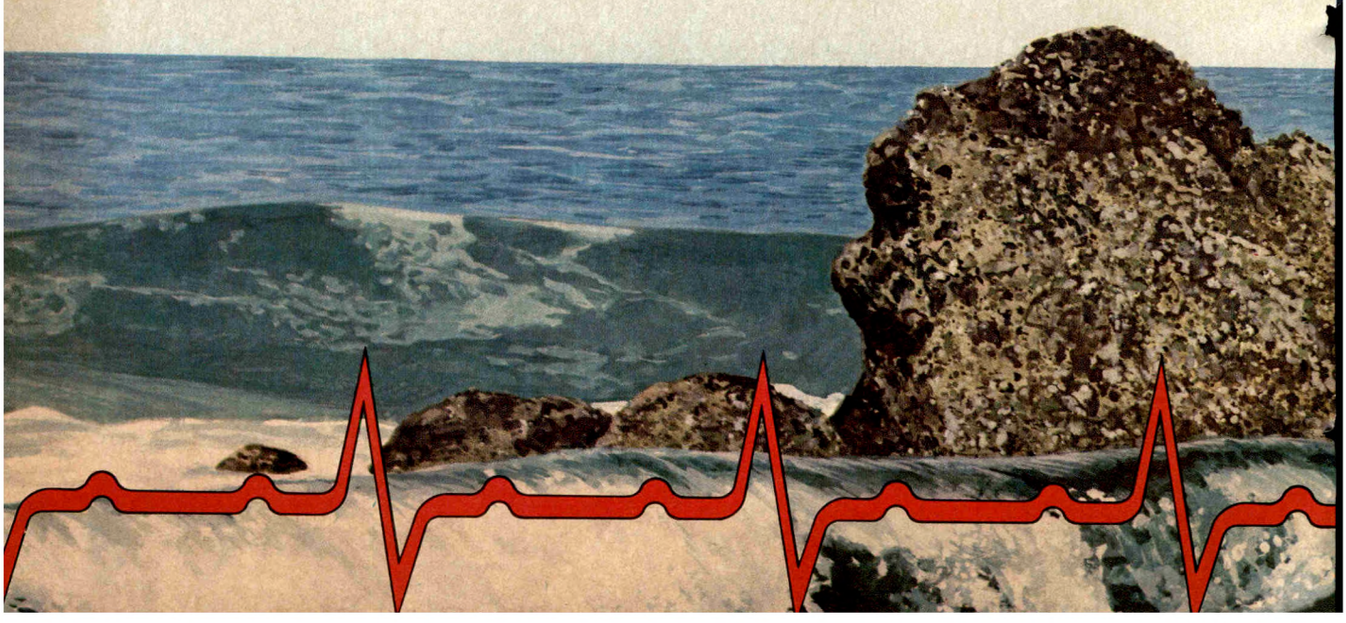
Avoids many late-onset toxicities encountered with other antiarrhythmics

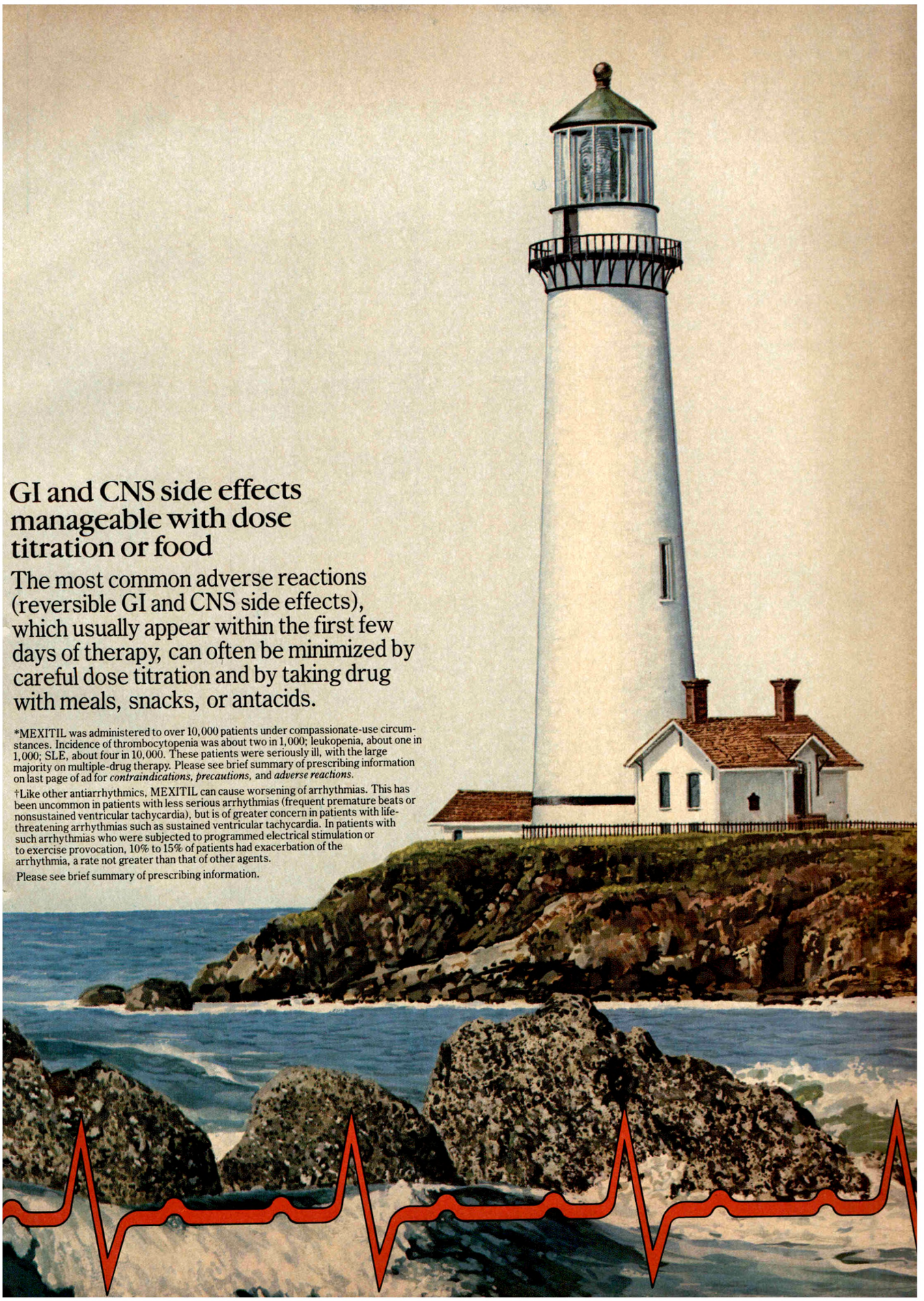
In controlled clinical trials, MEXITIL has not been associated with serious, late-onset toxicities such as hematologic effects, SLE, or pulmonary fibrosis.*

A favorable electrophysiologic and hemodynamic profile

MEXITIL is unlikely to aggravate arrhythmias in the clinical setting.[7-9†] It does not prolong the QT interval and, thus, is less likely than many other antiarrhythmics to produce torsades de pointes.[10,11]

MEXITIL has no significant negative inotropic effect, making it an excellent choice for use in patients with compromised cardiac function.[12-15]





GI and CNS side effects manageable with dose titration or food

The most common adverse reactions (reversible GI and CNS side effects), which usually appear within the first few days of therapy, can often be minimized by careful dose titration and by taking drug with meals, snacks, or antacids.

*MEXITIL was administered to over 10,000 patients under compassionate-use circumstances. Incidence of thrombocytopenia was about two in 1,000; leukopenia, about one in 1,000; SLE, about four in 10,000. These patients were seriously ill, with the large majority on multiple-drug therapy. Please see brief summary of prescribing information on last page of ad for *contraindications, precautions,* and *adverse reactions.*

†Like other antiarrhythmics, MEXITIL can cause worsening of arrhythmias. This has been uncommon in patients with less serious arrhythmias (frequent premature beats or nonsustained ventricular tachycardia), but is of greater concern in patients with life-threatening arrhythmias such as sustained ventricular tachycardia. In patients with such arrhythmias who were subjected to programmed electrical stimulation or to exercise provocation, 10% to 15% of patients had exacerbation of the arrhythmia, a rate not greater than that of other agents.

Please see brief summary of prescribing information.

MEXITIL®
(MEXILETINE HCl)

Distinguished by Its Safety Profile

References: 1. Data on file. Boehringer Ingelheim Pharmaceuticals, Inc. 2. Trimarco B, et al: *Curr Ther Res* 1983;33(3):472–487. 3. Singh JB, et al: *Am J Cardiol* 1984;53:84–87. 4. Fenster PE, Hanson CD: *Clin Pharmacol Ther* 1983;34(2):136–142. 5. Hession M, et al: *J Am Coll Cardiol* 1986;7(2):338–343. 6. Thompson KA, et al: *Clin Res* 1985;33(2):289A. 7. Velebit V, et al: *Circulation* 1982;65(5):886–894. 8. Podrid PJ, et al: *Am J Cardiol* 1987;59:38E–44E. 9. Campbell RWF: *Am J Cardiol* 1987;59:49E–51E. 10. Zipes DP: *Am J Cardiol* 1987;59:26E–31E. 11. Stratmann HG, Kennedy HL: *Am Heart J* 1987;113:1470–1482. 12. Sami M, Lisbona R: *Can J Cardiol* 1985;1(4):251–258. 13. Stein J, Podrid P, Lown B: *Am J Cardiol* 1984;54:575–578. 14. Shanks RG: *Am Heart J* 1984;107:1065–1071. 15. Chadda KD, Weiss P, Bodenheimer MM: *Circulation* 1987;76(suppl 4):IV–179, abstract 0712.

Mexitil®
(mexiletine hydrochloride)
Oral Antiarrhythmic

Capsules of 150 mg, 200 mg and 250 mg

Brief Summary of Prescribing Information

CONTRAINDICATIONS: Mexitil® (mexiletine hydrochloride) is contraindicated in the presence of cardiogenic shock or pre-existing second- or third-degree AV block (if no pacemaker is present).

PRECAUTIONS: General: If a ventricular pacemaker is operative, patients with second or third degree heart block may be treated with Mexitil® (mexiletine hydrochloride) if continuously monitored. A limited number of patients (45 of 475 in controlled clinical trials) with pre-existing first degree AV block were treated with Mexitil; none of these patients developed second or third degree AV block. Caution should be exercised when it is used in such patients or in patients with pre-existing sinus node dysfunction or intraventricular conduction abnormalities.

Like other antiarrhythmics Mexitil can cause worsening of arrhythmias. This has been uncommon in patients with less serious arrhythmias (frequent premature beats or non-sustained ventricular tachycardia: see ADVERSE REACTIONS), but is of greater concern in patients with life-threatening arrhythmias such as sustained ventricular tachycardia. In patients with such arrhythmias subjected to programmed electrical stimulation or to exercise provocation, 10-15% of patients had exacerbation of the arrhythmia, a rate not greater than that of other agents.

Mexitil should be used with caution in patients with hypotension and severe congestive heart failure. Since Mexitil is metabolized in the liver, and hepatic impairment has been reported to prolong the elimination half-life of Mexitil, patients with liver disease should be followed carefully while receiving Mexitil. The same caution should be observed in patients with hepatic dysfunction secondary to congestive heart failure.

Concurrent drug therapy or dietary regimens which may markedly alter urinary pH should be avoided during Mexitil therapy. The minor fluctuations in urinary pH associated with normal diet do not affect the excretion of Mexitil.

SGOT Elevation and Liver Injury: In three-month controlled trials, elevations of SGOT greater than three times the upper limit of normal occurred in about 1% of both mexiletine-treated and control patients. Approximately 2% of patients in the mexiletine compassionate use program had elevations of SGOT greater than or equal to three times the upper limit of normal. These elevations frequently occurred in association with identifiable clinical events and therapeutic measures such as congestive heart failure, acute myocardial infarction, blood transfusions and other medications. These elevations were often asymptomatic and transient, usually not associated with elevated bilirubin levels and usually did not require discontinuation of therapy. Marked elevations of SGOT (>1000 U/L) were seen before death in four patients with end-stage cardiac disease (severe congestive heart failure, cardiogenic shock).

In foreign marketing experience rare instances of severe liver injury, including hepatic necrosis, have been reported in association with Mexitil treatment. It is recommended that patients in whom an abnormal liver test has occurred, or who have signs or symptoms suggesting liver dysfunction, be carefully evaluated. If persistent or worsening elevation of hepatic enzymes is detected, consideration should be given to discontinuing therapy.

Blood Dyscrasias: Blood dyscrasias were not seen in the controlled trials. Among 10,867 patients treated with mexiletine in the compassionate use program, marked leukopenia (neutrophils less than 1000/mm^3) or agranulocytosis were seen in 0.06%, and milder depressions of leukocytes were seen in 0.08%, and thrombocytopenia was observed in 0.16%. Many of these patients were seriously ill and receiving concomitant medications with known hematologic adverse effects. Rechallenge with mexiletine in several cases was negative. Marked leukopenia or agranulocytosis did not occur in any patient receiving Mexitil alone; five of the six cases of agranulocytosis were associated with procainamide (sustained release preparations in four) and one with vinblastine. If significant hematologic changes are observed, the patient should be carefully evaluated, and, if warranted, Mexitil should be discontinued. Blood counts usually return to normal within one month of discontinuation. (See ADVERSE REACTIONS.)

Convulsions (seizures) did not occur in Mexitil controlled clinical trials. In the compassionate use program, convulsions were reported in about 2 of 1000 patients. Twenty-eight percent of these patients discontinued therapy. Convulsions were reported in patients with and without a prior history of seizures. Mexiletine should be used with caution in patients with known seizure disorder.

Drug Interactions: In a large compassionate use program Mexitil has been used concurrently with commonly employed antianginal, antihypertensive, and anticoagulant drugs without observed interactions. A variety of antiarrhythmics such as quinidine or propranolol were also added, sometimes with improved control of ventricular ectopy. When phenytoin or other hepatic enzyme inducers such as rifampin and phenobarbital have been taken concurrently with Mexitil, lowered Mexitil plasma levels have been reported. Monitoring of Mexitil plasma levels is recommended during such concurrent use to avoid ineffective therapy.

In a formal study, benzodiazepines were shown not to affect Mexitil plasma concentrations. ECG intervals (PR, QRS and QT) were not affected by concurrent Mexitil and digoxin, diuretics, or propranolol.

Concurrent administration of cimetidine and Mexitil has been reported to increase, decrease, or leave unchanged Mexitil plasma levels; therefore patients should be followed carefully during concurrent therapy.

Mexitil does not alter serum digoxin levels, but magnesium-aluminum hydroxide, when used to treat gastrointestinal symptoms due to Mexitil, has been reported to lower serum digoxin levels.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Studies of carcinogenesis in rats (24 months) and mice (18 months) did not demonstrate any tumorigenic potential. Mexitil was found to be non-mutagenic in the Ames test. Mexitil did not impair fertility in the rat.

Pregnancy/Teratogenic Effects

Pregnancy Category C: Reproduction studies performed with Mexitil in rats, mice and rabbits at doses up to four times the maximum human oral dose (20 mg/kg in a 50 kg patient) revealed no evidence of teratogenicity or impaired fertility but did show an increase in fetal resorption. There are no adequate and well-controlled studies in pregnant women; this drug should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Mexitil appears in human milk in concentrations similar to those observed in plasma. Therefore, if the use of Mexitil is deemed essential, an alternative method of infant feeding should be considered.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Mexitil® (mexiletine hydrochloride) commonly produces reversible gastrointestinal and nervous system adverse reactions but is otherwise well tolerated. Mexitil has been evaluated in 483 patients in one-month and three-month controlled studies and in over 10,000 patients in a large compassionate use program. Dosages in the controlled studies ranged from 600-1200 mg/day; some patients (8%) in the compassionate use program were treated with higher daily doses (1600-3200 mg/day). In the three-month controlled trials comparing Mexitil to quinidine, procainamide and disopyramide, the most frequent adverse reactions were upper gastrointestinal distress (41%), lightheadedness (10.5%), tremor (12.6%) and coordination difficulties (10.2%). Similar frequency and incidence were observed in the one-month placebo-controlled trial. Although these reactions were generally not serious, and were dose-related and reversible with a reduction in dosage, by taking the drug with food or antacid or by therapy discontinuation, they led to therapy discontinuation in 40% of patients in the controlled trials. A tabulation of the adverse events reported in the one-month placebo-controlled trial follows:

Comparative Incidence (%) of Adverse Events among Patients Treated with Mexiletine and Placebo in the 4-Week, Double-Blind Crossover Trial

	Mexiletine N=53	Placebo N=49
Cardiovascular		
Palpitations	7.5	10.2
Chest Pain	7.5	4.1
Increased Ventricular Arrhythmias/PVC's	1.9	—
Digestive		
Nausea/Vomiting/Heartburn	39.6	6.1
Central Nervous System		
Dizziness/Lightheadedness	26.4	14.3
Tremor	13.2	—
Nervousness	11.3	6.1
Coordination Difficulties	9.4	—
Changes in Sleep Habits	7.5	16.3
Paresthesias/Numbness	3.8	2.0
Weakness	1.9	4.1
Fatigue	1.9	2.0
Tinnitus	1.9	4.1
Confusion/Clouded Sensorium	1.9	2.0
Other		
Headache	7.5	6.1
Blurred Vision/Visual Disturbances	7.5	2.0
Dyspnea/Respiratory	5.7	10.2
Rash	3.8	2.0
Non-specific Edema	3.8	—

A tabulation of adverse reactions occurring in one percent or more of patients in the three-month controlled studies follows:

Comparative Incidence (%) of Adverse Events among Patients Treated with Mexiletine or Control Drugs in the 12-Week, Double-Blind Trials

	Mexiletine N=430	Quinidine N=262	Procainamide N=78	Disopyramide N=69
Cardiovascular				
Palpitations	4.3	4.6	1.3	5.8
Chest Pain	2.6	3.4	1.3	2.9
Angina/Angina-like Pain	1.7	1.9	2.6	2.9
Increased Ventricular Arrhythmias/PVC's	1.0	2.7	2.6	—
Digestive				
Nausea/Vomiting/Heartburn	39.3	21.4	33.3	14.5
Diarrhea	5.2	33.2	2.6	8.7
Constipation	4.0	—	6.4	11.6
Changes in Appetite	2.6	1.9	—	—
Abdominal Pain/Cramps/Discomfort	1.2	1.5	—	1.4
Central Nervous System				
Dizziness/Lightheadedness	18.9	14.1	14.1	2.9
Tremor	13.2	2.3	3.8	1.4
Coordination Difficulties	9.7	1.1	1.3	—
Changes in Sleep Habits	7.1	2.7	11.5	8.7
Weakness	5.0	5.3	7.7	2.9
Nervousness	5.0	1.9	6.4	5.8
Fatigue	3.8	5.7	5.1	1.4
Speech Difficulties	2.6	0.4	—	—
Confusion/Clouded Sensorium	2.6	—	3.8	—
Paresthesias/Numbness	2.4	2.3	2.6	—
Tinnitus	2.4	1.5	—	—
Depression	2.4	1.1	1.3	1.4
Other				
Blurred Vision/Visual Disturbances	5.7	3.1	5.1	7.2
Headache	5.7	6.9	7.7	4.3
Rash	4.2	3.8	10.3	1.4
Dyspnea/Respiratory	3.3	3.1	5.1	2.9
Dry Mouth	2.8	1.9	5.1	14.5
Arthralgia	1.7	2.3	5.1	1.4
Fever	1.2	3.1	2.6	—

Less than 1%: Syncope, edema, hot flashes, hypertension, short-term memory loss, loss of consciousness, other psychological changes, diaphoresis, urinary hesitancy/retention, malaise, impotence/decreased libido, pharyngitis.

An additional group of over 10,000 patients has been treated in a program allowing administration of Mexitil under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy. Twenty-four percent of the patients continued in the program for one year or longer. Adverse reactions leading to therapy discontinuation occurred in 15% of patients (usually upper gastrointestinal system or nervous system effects). In general, the more common adverse reactions were similar to those in the controlled trials. Less common adverse events possibly related to Mexitil use include:

Cardiovascular System: Syncope and hypotension, each about 6 in 1000; bradycardia, about 4 in 1000; angina/angina-like pain, about 3 in 1000; edema, atrioventricular block/conduction disturbances and hot flashes, each about 2 in 1000; atrial arrhythmias, hypertension and cardiogenic shock, each about 1 in 1000.

Central Nervous System: Short-term memory loss, about 9 in 1000 patients; hallucinations and other psychological changes, each about 3 in 1000; psychosis and convulsions/seizures, each about 2 in 1000; loss of consciousness, about 6 in 10,000.

Digestive: Dysphagia, about 2 in 1000; peptic ulcer, about 8 in 10,000; upper gastrointestinal bleeding, about 7 in 10,000; esophageal ulceration, about 1 in 10,000.

Laboratory: Abnormal liver function tests, about 5 in 1000 patients; positive ANA and thrombocytopenia, each about 2 in 1000; leukopenia (including neutropenia and agranulocytosis), about 1 in 1000; myelofibrosis, about 2 in 10,000 patients.

Other: Diaphoresis, about 6 in 1000; altered taste, about 5 in 1000; salivary changes, hair loss and impotence/decreased libido, each about 4 in 1000; malaise, about 3 in 1000; urinary hesitancy/retention, each about 2 in 1000; hiccups, dry skin, laryngeal and pharyngeal changes and changes in oral mucous membranes, each about 1 in 1000; SLE syndrome, about 4 in 10,000.

Hematology: Blood dyscrasias were not seen in the controlled trials but did occur among the 10,867 patients treated with mexiletine in the compassionate use program: (See PRECAUTIONS). Myelofibrosis was reported in two patients in the compassionate use program; one was receiving long-term thiotepa therapy and the other had pretreatment myeloid abnormalities.

HOW SUPPLIED:
Mexitil® (mexiletine hydrochloride) is supplied in hard gelatin capsules containing 150, 200 or 250 mg of mexiletine hydrochloride in bottles of 100 and individually blister-sealed unit-dose cartons of 100.

Consult package insert before prescribing.

ME-4063

ME-BS-4/87

Boehringer Ingelheim

Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877

Coronary Artery Disease in Women

ELAINE D. EAKER, ScD, BARBARA PACKARD, MD, PhD, NANETTE K. WENGER, MD, THOMAS B. CLARKSON, DVM, and H.A. TYROLER, MD

Diseases of the heart are the leading cause of death among women in the U.S. and account for about 28% of all deaths in women. Of the 550,000 people who die each year in the U.S. from heart-related diseases, >250,000 are women. Because coronary artery disease (CAD) is less common in women, it has not been as thoroughly studied in women as in men. Results from studies of men have frequently been generalized to women, which may not be appropriate.

The National Heart, Lung, and Blood Institute Workshop on Coronary Heart Disease in Women, held in Bethesda, Maryland, January 26 to 28, 1986, convened scientists from the disciplines of epidemiology, atherosclerosis and clinical cardiology who have studied or have access to data about CAD in women. The workshop was designed to delineate the current state of knowledge about CAD in women and to define issues and questions that need further study, areas where information is lacking and needs and opportunities for research. Three aspects of CAD in women were discussed: (1) epidemiologic data on the prevalence and risk of fatal and nonfatal CAD, (2) pathophysiologic processes of atherogenesis that may be unique to women and (3) clinical aspects of CAD in women. The following is a summary of the workshop deliberations in each of these areas.

Epidemiologic Data: Fatal and Nonfatal Coronary Artery Disease in Women

Of the 250,000 women who die from CAD each year in the U.S. 100,000 of these deaths are premature (before average age of life expectancy). Although CAD is the leading cause of death in both black and white U.S. women, black women have a higher CAD mortality rate, especially in the younger age groups.

From the National Heart, Lung, and Blood Institute, Bethesda, Maryland, Emory University, Atlanta, Georgia, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, and the University of North Carolina, Chapel Hill, North Carolina. Manuscript received October 15, 1987; revised manuscript received and accepted November 6, 1987.

Address for reprints: Elaine D. Eaker, ScD, Epidemiology and Biometry Program National Heart, Lung, and Blood Institute, Federal Building, Room 2c08, Bethesda, Maryland 20892.

The 37% decrease in CAD mortality between 1963 and 1983 was similar for men and women. From 1968 to 1978 the percent of decrease in CAD mortality was greater among women that men, but the reverse was true from 1979 to 1983. Black women had the greatest rate of decrease in CAD mortality of any sex-race group from 1968 to 1978, but the smallest rate of decrease from 1979 to 1983. Despite this consistent decrease in the CAD death rates, marked geographic differences are evident. Clusters of high CAD death rate areas for women as well as men are present in the mid-Atlantic states of New York, New Jersey, Pennsylvania, Ohio, Kentucky and West Virginia; the western mountain states have the lowest quartile of CAD death rates in women. There is a wide range in international CAD death rates among women aged 40 to 69 years. In Scotland and Ireland the rates for 1980 were approximately 200/100,000, whereas in France and Japan the rates were about 25/100,000. However, a consistent trend of decreasing CAD death rates in women between 1950 and 1978 is present in industrialized countries.

Although U.S. women experience less than half the age-adjusted mortality rate from CAD as men, women generated 58% of total expenditures for heart disease—$7.6 billion in 1980. Women, in general, recognize and report systemic hypertension more often than men, although the prevalence of hypertension is greater among men through 55 years of age. Black women have a greater prevalence of hypertension than do white women, and report seeking care more frequently. Reports of all cardiovascular diseases were greater among women than would be expected from epidemiologic studies, indicating a greater awareness of these diseases by women. In addition, women reported cardiovascular disease as a problem as often as or more frequently than men. Women make more ambulatory care visits for cardiovascular diseases than do men; however, hospital admission rates do not differ by gender. Women receive more medical attention for cardiovascular diseases than do men. They also generally report more restricted activity than men, but no greater inability to work due to cardiovascular disease.

The potential risk factors for CAD in women can be divided into characteristics shared by both women and

men (e.g., increased age, systemic hypertension, cigarette smoking, levels of certain plasma lipoproteins, diabetes mellitus and obesity) and those pertinent only to women (e.g., oral contraceptive use, menopause, hysterectomy and exogenous hormone use). Estimates of the levels and distributions of coronary risk factors in the U.S. are available from surveys of the National Center of Health Statistics. Based on the National Health and Nutrition Examination Survey II (1976 to 1980), 25% of white women and 38% of black women aged 18 to 74 years have hypertension (defined as systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg, and also including women taking blood pressure medication). In the late 1970s, about one-fourth of all white women aged 25 to 74 years had high risk serum cholesterol levels (defined as >220 mg/dl for women aged 20 to 29, >240 for women aged 30 to 39 and >260 for women aged 40+). In 1983, 29% of women 20 years of age and older were cigarette smokers. Women in this age group have only slightly decreased their cigarette smoking from 1965 to 1983. Among women aged 20 to 29 years, however, cigarette smoking has increased from 1980 to 1983.

Most evidence relating individual attributes to the development of CAD has been derived predominantly from analyses done in men. Many studies, however, also included data from women; multivariate analyses of these data showed that increased age, cigarette smoking, systemic hypertension, diabetes mellitus or glucose intolerance contributed to the risk of CAD in women. Elevated total and low density lipoprotein cholesterol levels are strong coronary risk factors and elevated high density lipoprotein cholesterol appears to be protective against CAD. Other factors that appeared in some studies to be associated with myocardial infarction or CAD in women include blood group A, family history of myocardial infarction, history of previous heart disease, chest pain, blood pressure medication and elevated triglyceride levels. Physical activity, vital capacity and social group membership are, in some studies, inversely related to CAD risk in women. Diabetes mellitus imparts a greater risk to women compared with men when the other risk factors are taken into account.

For characteristics unique to women, most studies indicate a 3- to 4-fold increase in risk of both fatal and nonfatal myocardial infarction in women using oral contraceptives; this risk increases among heavy cigarette smokers. The risk of myocardial infarction among past users of oral contraceptives appears similar to that of women who never used oral contraceptives.

The effect of menopausal status on CAD risk is unclear. Before natural menopause, CAD rates are very low, but increase rapidly with menopause. Little evidence exists, however, that menopause per se or the attendant changes in hormones and lipids are responsible for the increased occurrence of CAD. The coronary risk associated with menopause is confounded by such variables as age of onset of menopause, natural versus surgical menopause and changing use of exogenous hormones. Most data indicate a protective association against CAD risk for use of noncontraceptive hormones in postmenopausal women; however, some studies show no effect or a detrimental association. The relation of reproductive status to CAD or atherosclerosis in women also remains unclear.

Most studies do not include data on psychosocial and behavior characteristics of women. Those studies with psychosocial information showed that lack of group membership was related to CAD mortality in women and that type A behavior was related to manifestations of CAD when angina pectoris was present.

Pathophysiologic Processes of Atherogenesis

In studies of human atherosclerosis, women of certain races and societies have substantially less CAD and coronary artery atherosclerosis during their reproductive years than do their male counterparts. White women have significantly fewer diseased coronary arteries than do black women.

Nonhuman primates, such as cynomolgus macaques, have been used as animal models to study atherosclerosis because they are similar to humans in gender differences regarding the extent of coronary artery atherosclerosis and gender differences in serum cholesterol concentrations. In addition, female cynomolgus macaques have a menstrual cycle similar to that of women. Ovarian function is a major factor associated with atherosclerosis in female cynomolgus macaques; ovarian function and concomitant endocrine function are markedly affected by social behavior, as subordinate macaque females often exhibit ovarian and endocrine deficiencies that are closely associated with atherosclerosis.

Interest has been growing in the relations among physical activity, lipid levels and CAD in women. Recent studies have shown that endurance training in women is associated with a decrease in circulating estrogen concentrations. The relation of exercise to high density lipoprotein cholesterol levels is inconsistent. The effects of exercise on plasma cholesterol and sex steroid concentrations have been studied in both pre- and postmenopausal women. Young women runners progressively increase their high density lipoprotein cholesterol concentration (independent of weight loss) and decrease their estrogen concentrations. Postmenopausal women have no significant changes in total plasma cholesterol, high density lipoprotein cholesterol or estrogen concentration after 8 months of exercise. Menopausal women do not appear to respond to exercise as do men and younger women; their level of exercise may not have been adequate to elicit a response or their low estrogen level may have rendered them insensitive to the effects of exercise on high density lipoprotein cholesterol.

Research scientists have speculated that cardiovascular and neuroendocrine hyperactivity to behavioral stimuli may be the biologic mechanism that predisposes individuals to coronary atherosclerosis. Women have significantly smaller epinephrine responses to common psychologic stressors than men do, but this

relation is largely behavioral in origin. When women are observed under stressful conditions that are personally "relevant" (in the sense that psychomotor and achievement-oriented tasks may be seen as relevant by men), women are as equally reactive as men. Some studies have shown more pronounced cardiovascular responses to stress in postmenopausal women, compared with age-matched premenopausal control subjects.

Because women are often prescribed hormonal steroids both for contraception and for menopausal symptoms, the effects of these hormonal steroids on lipoprotein levels and atherogenesis are of interest. The use of estrogen-progesterone oral contraceptives increases low density lipoprotein cholesterol levels; this increase varies with different preparations, particularly those containing higher hormone doses. Therapy with postmenopausal estrogens in "replacement" doses decreases both intermediate low density lipoprotein and low density lipoprotein levels; high density lipoprotein levels increase, particularly the high density lipoprotein$_2$ subfraction. There is little evidence that cyclic progestogen and estrogen use affects lipoprotein levels.

Clinical Aspects of Coronary Artery Disease in Women

Although CAD accounts for one-third of all deaths among women, evaluation of medical therapies for women with CAD has been limited. First coronary events are more often fatal in women (39%) than in men (31%). Excluding fatalities, the initial manifestations of CAD are strikingly dissimilar: 50% of men present with myocardial infarction compared with 34% of women. Angina pectoris is described as the initial manifestation of CAD in 55% of women compared with 43% of men. Angiographic studies demonstrate that fewer than 50% of women presenting with chest pain have coronary artery obstructive lesions, casting doubt on epidemiologic data based on chest pain (angina) history without angiographic confirmation or occurrence of a definite CAD event.

Studies of the relation of coronary artery atherosclerosis to chest pain in white men and women show that all subgroups of men with chest pain have a greater than 50% prevalence of coronary stenosis, whereas only those subgroups of women with Canadian Heart Association class III and IV angina have a majority with such stenoses. The lower prevalence of CAD in women and the equal or higher prevalence of noncardiac causes of chest pain lead to a high rate of false-positive diagnoses of CAD in women with chest pain. While the clinical manifestations of CAD are similar in men and women, the noninvasive diagnosis of CAD in women presents a major problem. The criteria for the diagnosis of CAD by various noninvasive procedures have been derived from populations of men and applied to women; however, the relatively low prevalence of CAD in women produces a higher ratio of false-positive to true-positive results.

Diagnostic outcome varies in women depending on their presenting symptoms. Women with definite classic angina pectoris have a high likelihood of underlying CAD. With probable angina pectoris, only about one-third of women will have CAD. Attempts have been made to improve the specificity and sensitivity of diagnostic exercise testing in women by using thallium myocardial imaging and radionuclide ventriculography. In the clinical evaluation of women with classic angina pectoris, the exercise electrocardiogram and cardiac fluoroscopy appear cost-effective in providing important diagnostic information that may preclude the need for further noninvasive testing in most patients. In women with probable angina pectoris, thallium exercise scintigraphy or cardiac fluoroscopy, or a combination of the 2, represent a better diagnostic choice than the exercise electrocardiogram alone, because of higher specificity with similar sensitivity.

The left ventricular mass and various indexes of it are significantly less in women than in men. When corrected for body mass, however, this difference disappears. Certain parameters of left ventricular function in women with CAD differ significantly from those of men with CAD. For example, the ejection fraction is significantly higher in women with CAD than in men with CAD. The effect of left ventricular dysfunction, however, on morbidity and mortality appears to be similar in men and women. The apparent better preoperative left ventricular function in women with CAD, however, does not translate into an improved outcome after coronary artery bypass graft surgery.

Post-infarction ventricular arrhythmias have been identified as important adverse prognostic characteristics in men. Data from the Multicenter Postinfarction Trial indicate that the significant association of frequent ventricular ectopy with 2-year mortality in men does not occur in women. In contrast, ejection fractions of <30% predicted mortality in both men and women.

Because women have a different endocrine response than men, their medication effects may differ. An important area of drug therapy with considerable data for women is antihypertensive therapy. Women describe more side effects from β-blocking drugs than do men. A possible explanation for the increased occurrence of side effects in women may be due to the fixed-dose therapy in most clinical trials. Women's reduced body mass may result in a relatively greater drug dose effect. Although women with hypertension live longer than hypertensive men, some studies have shown that antihypertensive therapy provides less benefit in preventing CAD among women, particularly white women compared with white men. This apparent reduced benefit is confounded by a number of factors, not the least of which is the lower overall morbidity and mortality from cardiovascular disease among women. Nevertheless, the same guidelines for the treatment of hypertension were considered appropriate for both men and women. Previous studies suggest that both short- and long-term effects of antihy-

pertensive therapy may differ in women; because the effectiveness varies for different cardiovascular endpoints (i.e., greater stroke benefit vs lesser CAD benefit), future studies should collect and analyze their data accordingly.

Both the efficacy and side effects of the 3 currently used classes of antianginal drugs—nitrates, β blockers and calcium antagonists—have been studied predominantly in men. Because women, in general, have smaller coronary arteries related to their smaller body size, fluctuations in coronary tone may be of increased importance. This suggests that nitrates and calcium antagonists may be preferred therapies. Nitrates and calcium antagonists are equally effective in treating patients with variant angina due to spasm.

From 1979 to 1984, the number of coronary artery bypass grafting procedures have more than doubled in women. Data from the Coronary Artery Surgery Study show that female sex predicted perioperative coronary artery bypass surgery mortality better than severity of angina or severity of left ventricular dysfunction. There were also large preoperative differences, such as body size, between men and women undergoing coronary artery bypass grafting that may have contributed to the differing outcomes. Women who survive the perioperative phase have a 5- and 10-year survival comparable to that of men, despite a lesser symptomatic improvement.

Percutaneous transluminal coronary angioplasty is a nonsurgical method of myocardial revascularization for selected patients with documented obstructive CAD. Short-term outcomes of this procedure in the early years, as documented in the Percutaneous Transluminal Coronary Angioplasty registry, indicated that female gender was an independent predictor of lower success and higher complication and mortality rates. This mortality difference is not evident in more recent series. In contrast to the less favorable short-term outcomes, after successful angioplasty women have comparable symptomatic improvement, a lower incidence of restenosis and need for revascularization and similar survival compared with men.

Following a myocardial infarction women are described as having more anxiety, depression and sexual dysfunction, and return to work less often than men. This raises the question of the effect of age on gender differences in response to a heart attack. Problems associated with widowhood, lack of social support, inadequate financial support and other concerns have not been systematically evaluated.

To obtain a copy of the full proceedings, please send requests and a payment of $35.00 to: Circulation Manager, Haymarket Doyma, Inc., 53 Park Place, New York, New York 10007

The National Heart, Lung, and Blood Institute Workshop on Coronary Heart Disease in Women

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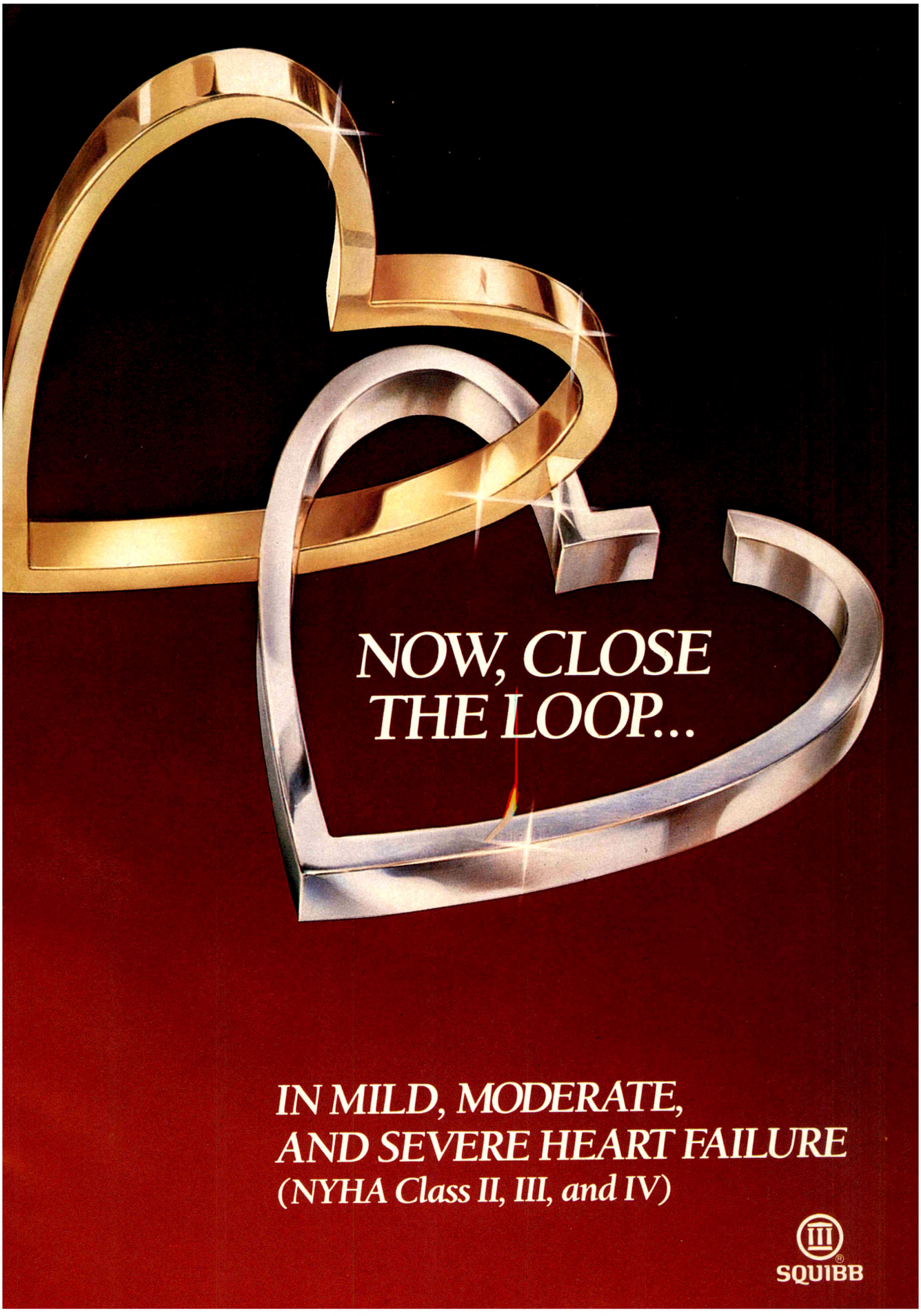
Participants: Michael R. Adams, DVM, Bowman Gray School of Medicine, Wake Forest University; Elizabeth Barrett-Connor, MD, University of California, San Diego; Martial Bourassa, MD, Montreal Heart Institute; Thomas W. Boyden, MD, VA Medical Center, Tucson; Katherine Detre, MD, PH, University of Pittsburgh; Frederick H. Epstein, MD, University of Zurich, Switzerland; Curt Furberg, MD, Bowman Gray School of Medicine, Wake Forest University; William R. Harlan, MD, University of Michigan; Michael V. Herman, MD, Westchester City Medical Center; Trudy L. Bush, PhD, Columbia University; William P. Castelli, MD, Framingham Heart Study, National Heart, Lung, and Blood Institute; Michael J. Cowley, MD, Medical College of Virginia; Kathryn Davis, PhD, University of Washington; Arthur J. Moss, MD, University of Rochester; William P. Newman, III, MD, Louisiana State University; Barbara L. Parry, MD, University of California, San Diego; Thomas A. Pearson, MD, PhD, Johns Hopkins University; Elliot Rapaport, MD, University of California, San Francisco; Millicent Higgins, MD, National Heart, Lung, and Blood Institute; Adolph M. Hutter, Jr., MD, Massachusetts General Hospital; William B. Kannel, MD, Boston University School of Medicine; Julian Keil, PH, Medical University of South Carolina; Luella Klein, MD, Emory University; Mary Grace Kovar, PH, National Center for Health Statistics; Ronald M. Krauss, MD, University of California, Berkeley; Paul E. Leaverton, PhD, University of South Florida; Stephen Manuck, PhD, University of Pittsburgh; Karen Matthews, PhD, University of Pittsburgh; Henry C. McGill, Jr., MD, University of Texas Health Science Center, San Antonia; Lois Monteiro, RN, PhD, Brown University; Robert Roberts, MD, Baylor College of Medicine; Lynn Rosenberg, ScD, Boston University; Stephen M. Schwartz, MD, PhD, University of Washington; Alvin P. Shapiro, MD, University of Pittsburgh; Meir J. Stampfer, MD, Harvard Medical School; Babette Stanton, PhD, Boston University School of Medicine; Peter H. Stone, MD, Harvard Medical School; Patricia Tennis, PhD, University of North Carolina; Thomas J. Thom, National Heart, Lung, and Blood Institute; David Waters, MD, Montreal Heart Institute; Deborah Wingard, PhD, University of California, San Diego.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*CAPOTEN is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. See INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS in the brief summary of prescribing information on last page.

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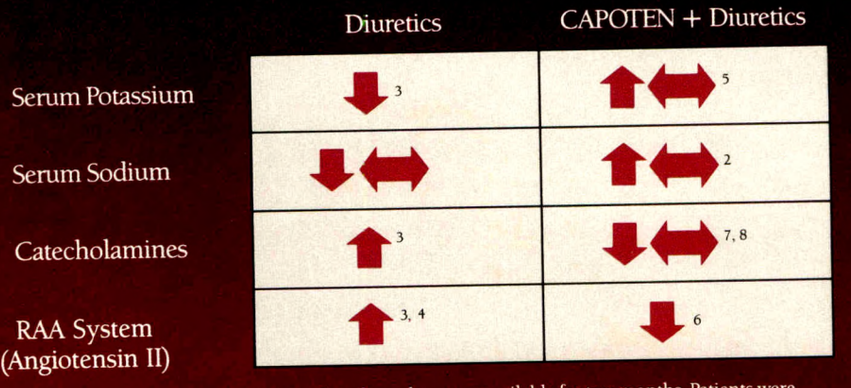

†Patients for whom data were available for two months. Patients were NYHA Class II, III, and IV receiving concomitant diuretic and digitalis therapy.

‡Fourteen patients were NYHA Class III and IV receiving concomitant diuretic and digitalis therapy.

IN MILD, MODERATE, AND SEVERE HEART FAILURE
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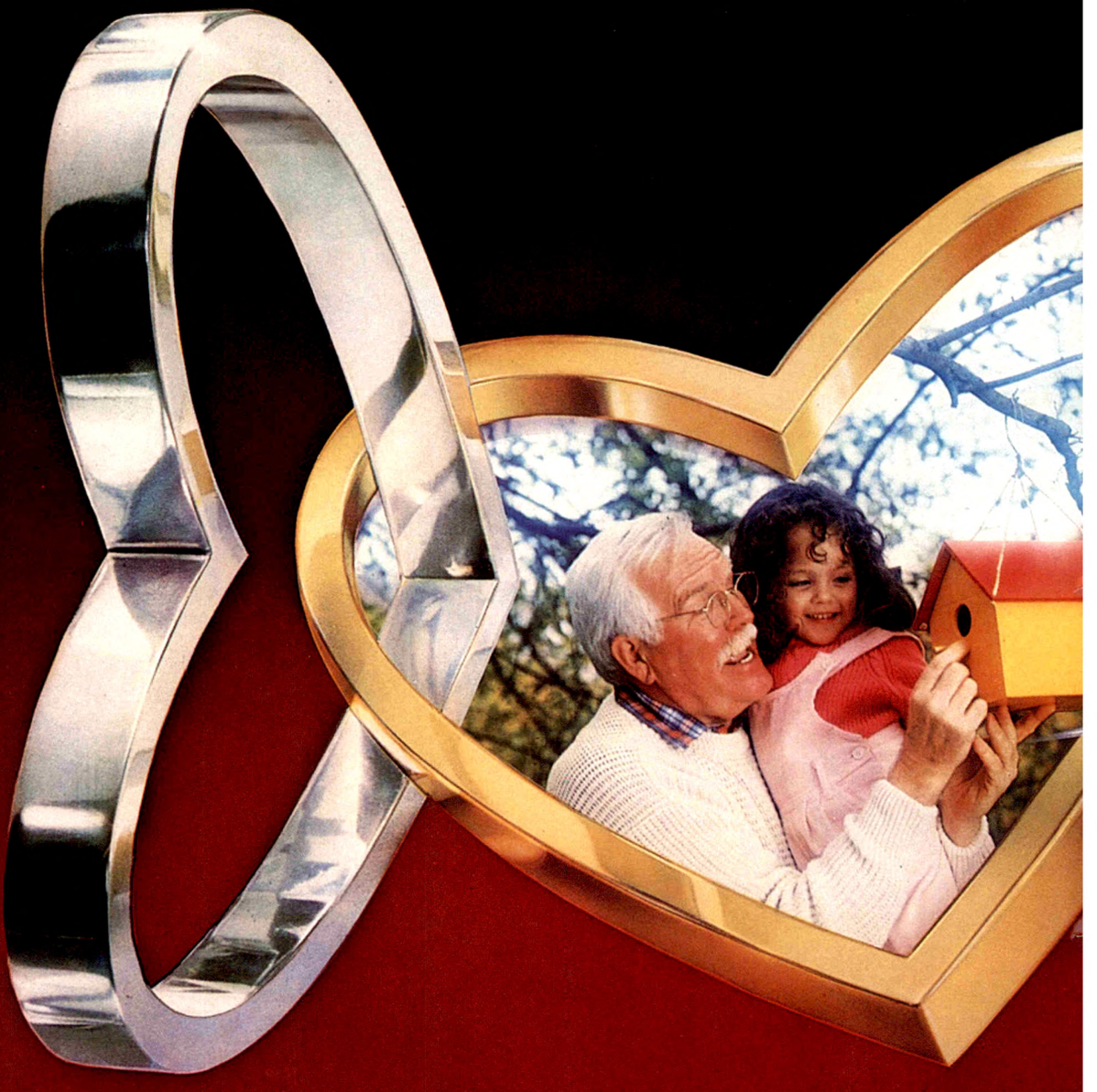

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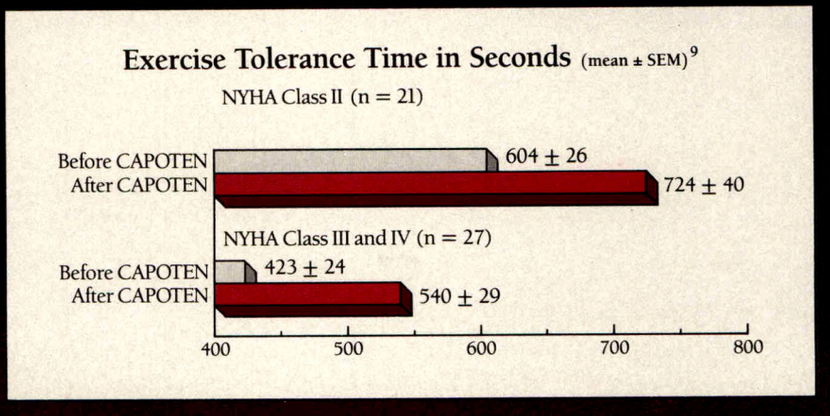

All patients were given diuretics and digitalis throughout the 12-week study period. Adapted from Captopril Multicenter Research Group.[9]

- Improves NYHA Class
  In the same study, patients (n = 49) experienced significant mean improvement in NYHA Class ($P < 0.001$)[9]
  - —Class II Patients (n = 22) improved from 2.5 to 2.1 (± 0.1)
  - —Class III and IV patients (n = 27) improved from 3.0 to 2.4

IN MILD, MODERATE, AND SEVERE HEART FAILURE
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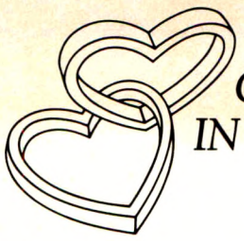

CLOSING THE LOOP IN HEART FAILURE THERAPY

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CAPOTEN® TABLETS

Captopril Tablets

INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia ($< 1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $< 1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* – Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* – If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension – Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

References:

1. The Captopril Multicenter Research Group I: Am Heart J 110:439-447, 1985. 2. Dzau VJ, Hollenberg NK: Ann Intern Med 100:777-782, 1984. 3. Packer M: Prim Cardiol, August 1987, pp 100-107. 4. Ikram H, Chan W, Espiner EA, et al: Clin Sci Mol Med 59:443-449, 1980. 5. Cleland JG, Dargie HJ, East BW, et al: Eur Heart J 6:681-688, 1985. 6. Dzau VJ: Drug Therapy, September 1986, pp 57-68. 7. Mettauer B., Rouleau J-L, Bichet D, et al: Circulation 73:492-502, 1986. 8. Cleland JGF, Dargie HJ, Hodsman GP, et al: Br Heart J 52:530-535, 1984. 9. Captopril Multicenter Research Group: J Am Coll Cardiol 2:755-763, 1983.

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Primary Coronary Artery Dissection Observed at Coronary Angiography

HIDEO NISHIKAWA, MD
SHIGEMOTO NAKANISHI, MD
SHINICHIRO NISHIYAMA, MD
SHIGEYUKI NISHIMURA, MD
AKIRA SEKI, MD
HIROSHI YAMAGUCHI, MD

Primary coronary artery dissection has rarely been reported since Pretty's first description in 1931.[1] Earlier cases, which were diagnosed incidentally at autopsy, yielded a clinical picture of catastrophic acute coronary artery disease, revealed either by sudden death (62%) or acute myocardial ischemia (38%).[2] Recently, however, the diagnosis has been made on clinical grounds. Among the 15 previous case reports of primary coronary artery dissection documented by coronary arteriogram (Table I), the diagnosis was made during coronary angiogram conducted for initial examination of acute myocardial infarction in 13 and during coronary angiogram performed under a diagnosis of angina pectoris in 2 patients.

We discovered 4 patients (0.28%) with primary coronary artery dissection among 1,445 consecutive patients with an angiographically final diagnosis of myocardial infarction (Table II). Primary coronary artery dissection may thus be more common than believed. Further, Shin et al[3] reported 2 cases of primary coronary artery dissection among 45 consecutive autopsied patients with cardiac diseases in the Sakurabashi Watanabe Hospital, Osaka. These results suggests that this entity may be more frequent in Japan.

Coronary angiograms of our 4 patients (Figures 1 to 5) revealed features common to all previous dissections: (1) a thin radiolucent line, that is, flap, indicating partial separation of the intima/media; (2) filling of the dissection sac; and (3) irregularity in caliber with widened or narrowed segments.[2] Reversibility of these changes is possible, and in follow-up studies, was particularly evident in dissections when reentry occurred spontaneously.[4] In case 2, we observed an angiographic return to relative patency of the segment of the right coronary artery, with partial resolution of the dissection (Figure 3), possibly reflecting thrombosis, retraction and dissolution of the dissection's hematoma in a manner similar to that demonstrated angiographically with aortic dissections.

Various hypotheses have been advanced to explain the etiology of primary coronary artery dissection. Preexisting coronary arteritis has frequently been described.[5] However, this change may simply be a response to the intramural hematoma rather than an underlying condition.[6] Histologic cystic medial necrosis has been reported more often, and Boschetti et al[7] took this as evidence of a preexisting brittleness of the media. Morise et al,[8] however, noted the same histologic features in 3 cases of iatrogenic coronary artery dissection. Bonnet et al[9] observed impaired collagen synthesis in an in vitro study of skin fibroblasts in a postpartum woman with primary coronary artery dissection. Low collagen synthesis may be responsible for an alteration in the mechanical function of vessel walls, leading to primary coronary artery dissection. The fre-

From the Division of Cardiology, Cardiovascular Center, Toranomon Hospital and the Department of Cardiology, School of Medicine, Juntendo University, Tokyo, Japan. Manuscript received July 16, 1987; revised manuscript received and accepted October 27, 1987.

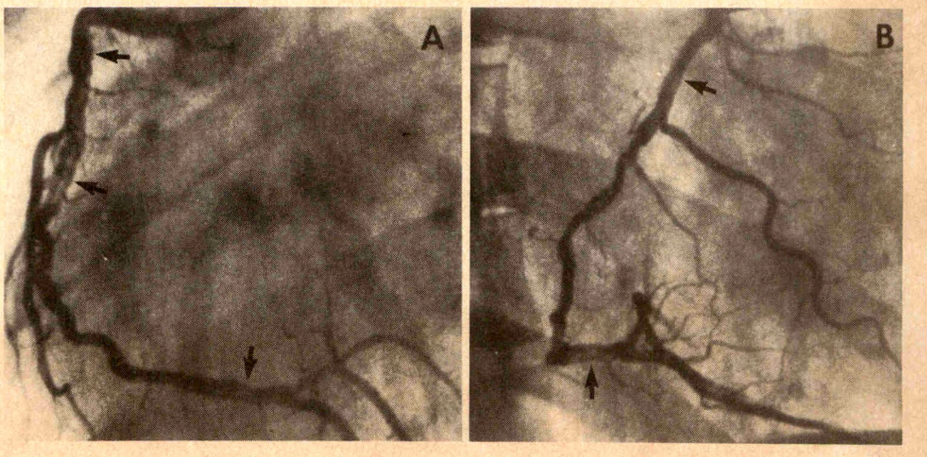

FIGURE 1. Right coronary arteriograms obtained in case 1. *A*, left anterior oblique projection; *B*, right anterior oblique projection. A dual lumen is present in the proximal to distal segment separated by a flap of intima/media (*arrows*).

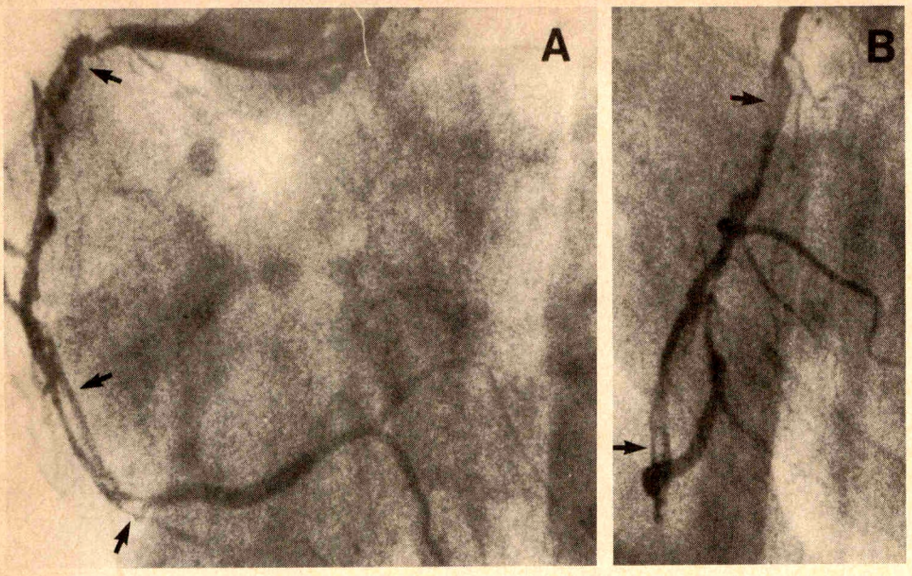

FIGURE 2. First right coronary arteriograms obtained in case 2. *A*, left anterior oblique projection; *B*, right anterior oblique projection. Severe wall irregularities with a dual lumen in the proximal to distal segment (*arrows*) are shown.

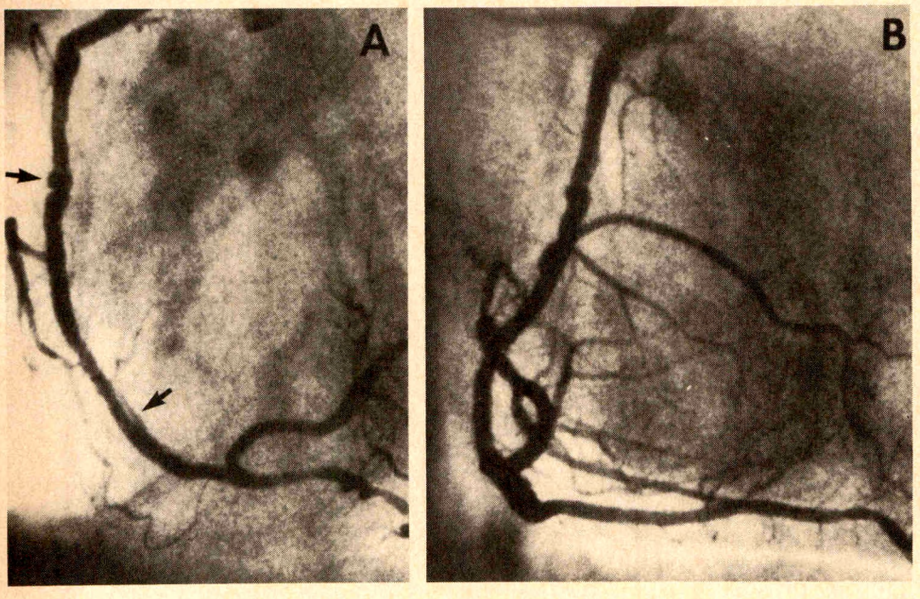

FIGURE 3. Repeat right coronary arteriograms obtained in case 2, 12 years later. *A*, left anterior oblique projection; *B*, right anterior projection. The previously noted right coronary artery dissection has resolved markedly with a well-demarcated perivascular pocket impinging on the wall of the vessel (*arrows*).

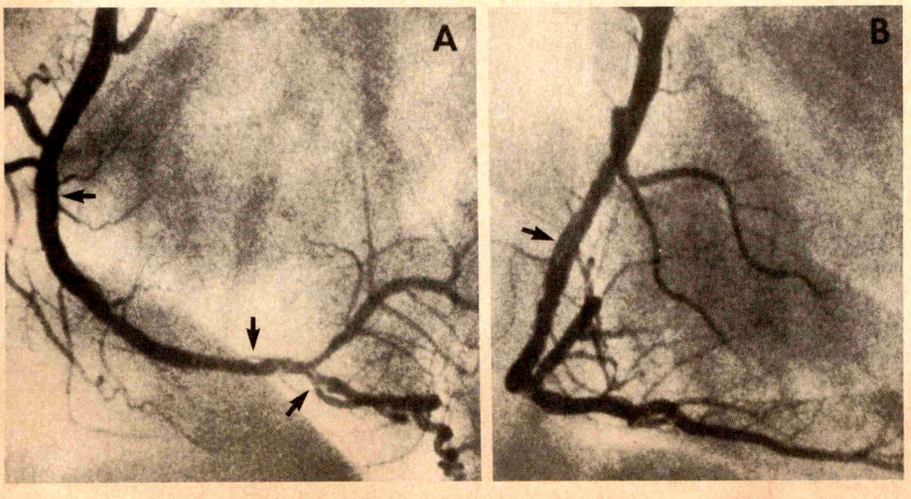

FIGURE 4. Right coronary arteriograms obtained in case 3. *A*, left anterior oblique projection; *B*, right anterior oblique projection. A dual lumen is present in the middle to distal segment and the proximal portion of the posterior descending branch is separated by a flap (*arrows*).

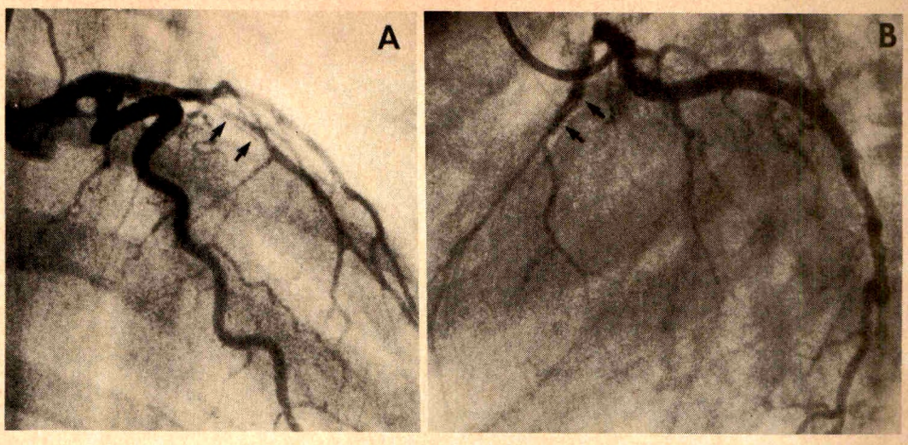

FIGURE 5. Left coronary arteriograms obtained in case 4. *A*, right anterior oblique projection; *B*, left anterior oblique projection. A flap-line defect is shown in the proximal to middle segment (*arrows*).

TABLE I Primary Coronary Artery Dissection Studied by Coronary Angiograms

Year, Study	Pt No.	Age (yr), Sex	Postpartum (days)	Artery Involved	Treatment
1973, Forker	1	56, M		Right	IMA implant
1975, Westbrook	2	26, F	0	LAD	Medical
1975, Razavi	3	31, F	6	LM, LAD, LC	Graft plus aneurysmectomy
1977, DiMatteo	4	59, F	0	Right	Graft
1977, Palank	5	31, M		Right	Medical
1978, Shaver	6	28, F	21	LM, LAD, LC	Medical
1978, Ciraulo	7	55, M		Right	Medical
1980, Molloy	8	42, F	0	LM, LAD, LC	Medical
1984, Mathieu	9	33, F	0	LAD	Medical
1985, Mark	10	50, F	0	Right	Medical
1985, DeJunco	11	52, M		Right	Graft
1985, Iskandrian	12	43, M		Right	—
	13	59, M		Right	—
	14	60, M		Right	—
1986, Bonnet	15	32, F	12, 2 mos	LC, LAD	Graft

IMA = internal mammary artery; LAD = left anterior descending; LC = left circumflex; LM = left main; 0 = negative; — = no information available.

TABLE II Patient Characteristics

Pt No.	Age (yr), Sex	Myocardial Infarction	Preexisting Vasospasm	Postpartum (days)	Artery involved	Treatment	Outcome after Infarction
1	28, M	Inferior	+		Right	Medical	Alive (6 yrs)
2	54, M	Inferior	+		Right	Medical	Alive (12 yrs)
3	46, F	Inferior	0	0	Right	Medical	Alive (3 yrs)
4	28, F	Anteroseptal	0	1	LAD	Medical	Died (4 yrs)

LAD = left anterior descending; + = positive; 0 = negative.

quency with which these dissections develop in young women, particularly during peripartum, as seen in case 4, may lend support to the role of hormones, because the association of pregnancy and aortic dissection is well known.[2] The report by Mark et al[10] of a patient with variant angina and angiographic evidence of primary coronary artery dissection is the only one of an association between variant angina and primary coronary artery dissection. However, we observed preexisting angina at rest, suggestive of variant angina, in cases 1 and 2. These 2 patients had no exertional chest pain. We assume that coronary vasospasm may have been the primary event. Variant angina has been described to occur more often in Japan, and may contribute to the prevalence of primary coronary artery dissection.

The treatment for primary coronary artery dissection has not been established because this disease was lethal in most previous patients (Table I). Surgical intervention was attempted in 5 patients: an internal mammary artery implant in 1, bypass and aneurysmectomy of the left ventricle in 1 and isolated bypass in 3. In the 11 remaining patients, including our 4, only medical treatment was attempted.

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Effect of Right Coronary Artery Occlusion During Percutaneous Transluminal Coronary Angioplasty on Right Ventricular Performance

MANFRED MAUSER, MD
KARL R. KARSCH, MD
LUDGER SEIPEL, MD

The effects of acute ischemia on left ventricular volumes and function have been studied extensively in animal models and, more recently, in patients with coronary artery disease during percutaneous transluminal coronary angioplasty (PTCA) of the left coronary artery.[1,2] Less attention, however, has been focused on the performance of the right ventricle in patients with chronic coronary artery disease or during acute occlusion of the right coronary artery (RCA). In patients with coronary artery disease, ischemia induced by balloon inflation during PTCA is a setting comparable to short-term coronary artery occlusion in the animal laboratory, and provides the opportunity to study the effects of acute ischemia on ventricular function in humans.

We describe the effects of acute ischemia on right ventricular (RV) performance in patients undergoing PTCA of the RCA.

Ten symptomatic patients with 1-vessel disease of the RCA without a history or electrocardiographic signs of a previous transmural myocardial infarction were studied. There were 7 men and 3 women with a mean age of 58 years (range 47 to 70). In each patient a single stenosis of at least 70% diameter reduction of the proximal RCA suitable for PTCA was documented by coronary angiography performed 1 or 2 weeks before investigation. All patients had a right dominant coronary artery circulation. The stenosis was either proximal (6 patients) or immediate distal (4) to the origin of the first RV branch, such that all ventricular branches were either distal to the balloon or occluded by the inflated balloon. The distal RCA was always filled anterograde and not by visible collaterals from the left coronary artery. The ventriculogram of the left ventricle showed a normal left ventricular wall motion in 9 patients and a severe hypokinetic diaphragmatic wall segment in 1 patient. All patients were receiving long-term therapy with calcium antagonists and long-acting nitrates. Two patients had additional β-blocker medication. No patient had significant valvular heart disease, evidence of pulmonary disease or unstable angina pectoris.

A 7Fr Swan-Ganz balloon-tipped catheter was advanced into the pulmonary artery via the left femoral vein. From the right femoral vein, a 7Fr pigtail catheter was placed into the right ventricle. Correct placement of the catheter was controlled by pressure recording. After basal pressure measurements a control ventriculogram with 10 ml of contrast material was obtained and the catheter position was corrected for a good opacification of the right ventricle without causing premature ventricular beats during injection. For pressure measurements fluid-filled Statham pressure transducers were used. For the biplane ventriculogram of the RV (30° right anterior oblique, 60° left anterior oblique) 40 ml of a nonionic contrast material (Ultravist 360, Schering Berlin) was injected into the RV with a flow of 10 ml/s and documented with a film speed of 50 frames/s. Standard PTCA equipment with a 9Fr arterial sheet within the right femoral artery was used. Balloon size of the dilatation catheter was selected according to the vessel diameter. A total of 3 to 5 occlusions were performed in each patient. The duration of each balloon inflation was 60 seconds. During the inflation period RV pressures, pulmonary artery pressure and heart rate were recorded. A second ventriculogram of the RV was performed at the end of the first occlusion period after at least 45 seconds of balloon inflation. The time interval between the 2 ventriculograms was at least 20 minutes. As noted by others, contrast medium has no persistent effect on hemodynamics within that time period. Care was taken to maintain the patients position unchanged and both ventriculograms were performed during inspiration. All patients gave their informed consent and there were no complications directly related to the research procedure.

The volumes of the right ventricle were analyzed according to the method described by Arcilla et al.[3] The regression equation was $y = 0.762x + 2.81$ *(x is the uncorrected and y the corrected volume). End-diastolic volume index, end-systolic volume index, stroke*

From the University Hospital, Department of Cardiology, Tuebingen, Federal Republic of Germany. Manuscript received August 18, 1987, revised manuscript received October 27, 1987, and accepted October 29.

TABLE I Hemodynamic Variables Before and at the End (60 Seconds) of Occlusion of the Right Coronary Artery

Pt		HR (l/min)	Systolic PAP (mm Hg)	Diastolic PAP (mm Hg)	RVEDP (mm Hg)	EDVI (ml/m²)	ESVI (ml/m²)	SVI (ml/m²)	EF (%)
1	Before	81	16	9	4	58	30	28	48
	End	74	24	12	8	73	58	15	21
2	Before	64	28	13	3	72	31	41	57
	End	57	33	21	7	92	59	33	36
3	Before	76	17	9	4	77	37	40	52
	End	84	17	10	8	80	47	33	41
4	Before	55	18	10	6	75	39	36	48
	End	48	18	9	11	87	56	31	36
5	Before	82	20	7	3	81	42	39	48
	End	78	21	8	8	96	68	28	29
6	Before	55	23	8	3	64	31	33	52
	End	84	40	16	7	95	58	37	39
7	Before	73	24	12	3	40	20	20	50
	End	68	23	11	12	71	49	22	31
8	Before	71	19	8	2	60	28	32	53
	End	80	21	7	6	79	48	31	39
9	Before	61	21	8	4	86	40	46	54
	End	60	28	9	8	103	80	23	22
10	Before	67	18	9	5	60	33	27	45
	End	63	20	9	8	69	47	22	32
	Before	68.5 ± 9.8	20.4 ± 3.7	9.3 ± 1.9	3.7 ± 1.2	67.3 ± 13.6	33.1 ± 6.6	34.2 ± 7.8	50.7 ± 3.6
	End	69.9 ± 12.3	24.5 ± 7.2	11.2 ± 4.3	8.3 ± 1.8†	84.5 ± 11.8	57.0 ± 10.5†	27.5 ± 6.8*	32.6 ± 7.0†

EDVI = end-diastolic volume index; ESVI = end-systolic volume index; EF = ejection fraction; HR = heart rate; PAP = pulmonary artery pressure; RVEDP = right ventricular end-diastolic pressure; SVI = stroke volume index.
* $p < 0.05$; † $p < 0.001$.

volume index and ejection fraction were calculated. Because ventricular volumes are influenced by the injected contrast material after 3 to 5 beats,[4] only the second or third beat after the onset of the injection was analyzed. Patients with premature ventricular contractions during the first beats were excluded from the study. Results are given as mean ± standard deviation. For statistical analysis Student paired t test was used.

Heart rate and the afterload of the right ventricle (pulmonary artery pressure) were not significantly influenced by the 60 second occlusion of the RCA (Table I). Right ventricular end-diastolic pressure increased significantly from 3.7 ± 1.2 to 8.3 ± 1.8 mm Hg ($p < 0.001$) and reached the elevated level after 24 ± 7 seconds. Together with the RV diastolic pressure the RV volumes increased markedly: end-diastolic volume index +25.5% ($p < 0.001$) and end-systolic volume index +72.2% ($p < 0.001$) (Table I). A significant decrease of the RV ejection fraction from 52 ± 3 to 33 ± 8% ($p < 0.001$) was found at the end of the balloon inflation period (Table I).

Several experimental studies have evaluated the effect of RCA occlusion on the RV hemodynamics. Brooks et al[5] demonstrated in a dog model that complete occlusion of the RCA at normal pulmonary artery pressures caused a decrease in RV contractile force without a change in RV filling pressure. In the pig,[6] whose coronary anatomy is more closely comparable to humans, total occlusion of the RCA produced a decrease of RV contractile force but also led to an increase of RV end-diastolic pressure. The described changes of RV function during ischemia were more pronounced if the pulmonary artery pressure was increased above normal values.[5]

In humans, Berger et al[7] studied the RV response to exercise in patients with coronary artery disease in a radionuclide ventriculography study. They described an abnormal exercise reserve of the right ventricle in these patients. RV dysfunction was independent of the presence or absence of a proximal RCA stenosis. Therefore they concluded that RV dysfunction during exercise is most likely due to an interaction between the left and right ventricle and not a consequence of RV ischemia due to a limited blood supply by the diseased RCA. In this study, however, no objective parameters of a RV ischemia were assessed, and ischemic dysfunction cannot easily be separated from ventricular interactions by morphologic parameters.

Ferlinz et al[8] described subnormal values of RV volumes (end-diastolic volume index = 61 ml/m²; stroke volume index = 33 ml/m² and ejection fraction = 52%) together with a normal end-diastolic pressure in patients with high-grade lesions of the RCA compared with patients with normal coronary arteries. Because pulmonary artery pressure and RV end-diastolic pressure were normal, these findings cannot easily be related to ischemia with decreased RV compliance or to RV afterload. Ferlinz et al[8] concluded that a reduced Frank-Starling effect may play a role in these patients.

The results of the present study—a reduced RV volume and ejection fraction together with normal RV filling pressures in patients with a significant stenosis of the RCA—are in good accordance with the findings of Ferlinz et al.[8] Acute short-term occlusion of the

RCA during PTCA results in a dramatic decrease of RV global function and a 38% decrease of RV ejection fraction. This is comparable to the response of the left ventricle to ischemia chamber volumes and end-diastolic pressure increases, which show a low tolerance of the human right ventricle even to short periods of ischemia. Therefore, in patients with an acute proximal occlusion of the RCA the clinical course may be influenced by the occurrence of RV failure.

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Recovery of Severe Ischemic Ventricular Dysfunction After Coronary Artery Bypass Grafting

DAVID A. BRILL, MD
LAWRENCE I. DECKELBAUM, MD
MICHAEL S. REMETZ, MD
ROBERT SOUFER, MD
JOHN A. ELEFTERIADES, MD
BARRY L. ZARET, MD

Ventricular wall motion abnormalities at rest are believed to be indicative of myocardial scar and fibrous tissue. Although patients may have reversible wall motion abnormalities at rest during periods of ischemia, recent evidence suggests that reversible ventricular dysfunction can persist after a major ischemic insult.[1,2] Braunwald and Rutherford[3] distinguish between stunned and hibernating myocardium and suggest that in either situation, revascularization can reverse exercise-induced ischemic dysfunction.[4,5] However, reversal of prolonged resting ventricular dysfunction is not as clear. We report a patient with severe coronary artery disease without myocardial infarction who had complete reversal of marked left ventricular (LV) dysfunction.

A 40-year-old man was healthy, physically active and free of any symptoms of cardiac dysfunction until 2 weeks before admission when he developed exertional dyspnea and angina pectoris. His symptoms increased, leading to hospitalization. He had had a pulmonary embolus at age 25 after knee surgery. His only medications were chlorpromazine 500 mg daily and temazepam 60 mg daily for post-traumatic stress disorder. He smoked a pack of cigarettes a day and had a

From the Department of Medicine, Cardiology Section, and the Department of Surgery, Yale University School of Medicine, New Haven, and the Veterans Administration Medical Center, West Haven, Connecticut. Manuscript received August 17, 1987; revised manuscript received and accepted October 27, 1987.

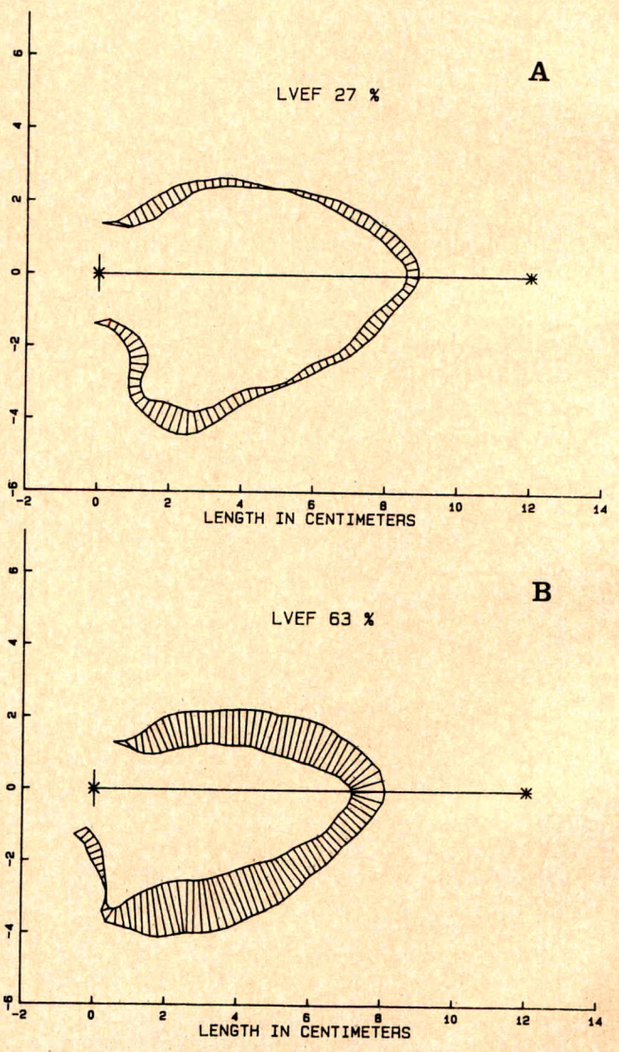

FIGURE 1. Left ventriculography before and after coronary artery bypass grafting. Diastolic and systolic ventricular outlines from right anterior oblique angiocardiograms are shown from the initial (*A*) and follow-up (*B*) catheterizations. Regional wall motion is represented by the chords that plot the excursion of each perimeter segment. Improved regional contraction involving all segments resulted in a global ejection fraction increase from 27% preoperatively to 63% 2 months postoperatively.

paternal family history of ischemic cardiac disease. He had bibasilar rales, a fourth heart sound and a soft systolic ejection murmur. The electrocardiogram revealed sinus rhythm at a rate of 95/min with biphasic T waves in leads I, aVL and V_4 through V_6. His chest x-ray was normal. He was admitted to the coronary care unit and was treated with lidocaine and nitroglycerin ointment. Serum creatine kinase levels remained within normal limits and his electrocardiogram did not change from admission. He had no further angina.

Cardiac catheterization on the third hospital day revealed globally depressed LV function with an ejection fraction of 27% (Figure 1A). He had a 90% diameter stenosis of the left main coronary artery. The right coronary, left circumflex and left anterior descending arteries had insignificant narrowings. An equilibrium radionuclide angiocardiogram on the same day revealed an LV ejection fraction of 17% with severe generalized hypokinesis. On the fourth hospital day he underwent coronary artery bypass grafting (CABG) with a left internal mammary graft to the left anterior descending artery and a saphenous vein graft to the left circumflex artery. At surgery, inspection of his heart revealed no evidence of acute myocardial infarction. He recovered uneventfully. A repeat equilibrium radionuclide angiocardiogram on the tenth hospital day revealed an LV ejection fraction of 36% without discrete regional wall motion abnormalities. The results of exercise tolerance test performed 5 weeks postoperatively were normal. An equilibrium radionuclide angiocardiogram performed 6 weeks postoperatively revealed an LV ejection fraction of 52%. The patient was readmitted to the hospital 8 weeks postoperatively with atypical chest pain and no electrocardiographic changes. Cardiac catheterization at that time revealed patent grafts and an LV ejection fraction of 63% (Figure 1B).

This report documents total reversal of severe global LV dysfunction as a result of CABG. Reversal of regional wall motion abnormalities at rest[4] and improvement in exercise LV ejection fraction[5] have been reported after CABG. However, the initial ejection fractions in these reports were normal or minimally abnormal and improved only modestly. Akins et al[6] reported 2 patients with previous history of myocardial infarction and severely depressed LV ejection fraction but without evidence of acute ischemia. Both patients had improvement in ejection fraction after revascularization (15 to 27% in 1 patient and 15 to 33% in the other). No previous report has documented complete reversal of severe LV dysfunction at rest following CABG. The improvement in ejection fraction over 6 weeks from 17 to 52% (an increase of 206%) in our patient is a dramatic example of the potential for reversible ischemic dysfunction.

The pathophysiology of persistent myocardial dysfunction in ischemic heart disease is not well understood. Matsuzaki et al[2] demonstrated in a dog model that prolonged partial occlusion of coronary arteries (5 hours) resulted in sustained myocardial dysfunction lasting several days before recovery. Braunwald and Kloner[1] in their review of stunned myocardium concluded that similar effects could be produced by repetitive ischemic episodes or brief total occlusion of the circulation. Ventricular dysfunction in our patient was most likely the result of either stunned myocardium secondary to an ischemic event, ongoing silent ischemia (hibernating myocardium) or both. The patient's repeated episodes of angina may have induced prolonged depression of systolic LV function. The recovery of LV dysfunction following CABG suggests that the myocardium was chronically ischemic and hibernating, not necrotic. The serial improvement in ejection fraction suggests myocardial stunning with the gradual return of function of postischemic reperfused myocardium.

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Allorhythmic Preexcitation due to Anterograde Concealed Kent Bundle Conduction

GAETANO SATULLO, MD
GIUSEPPE ORETO, MD
FRANCESCO LUZZA, MD
GIUSEPPE PALEOLOGO, MD
LEO SCHAMROTH, MD

Intermittent preexcitation is due to intermittent block of the impulse within the accessory pathway.[1] When such intermittency occurs, the preexcitation complexes usually appear in an irregular distribution pattern. We report an unusual, hitherto undescribed, distribution pattern that can be explained on the basis of concealed trigeminal preexcitation.

The electrocardiogram (Figure 1), part of a 6-minute continuous recording, was recorded from a 34-year-old woman with the Wolff-Parkinson-White syndrome. The tracing reflects intermittent preexcitation. There are QRS complexes that are narrow and associated with a normal PR interval, and others that have a delta wave and a short PR interval. The distribution of the preexcitation complexes, however, is not haphazard but conforms with an unusual but distinct pattern. Thus, the normal complexes that intervene between 2 successive preexcitation beats are almost always in numbers of 2, 5 or 8 (Figure 1, Table I). In a further section of the recording, however, a few exceptions did occur where the intervening normal beats were in numbers of 1, 4 or 10 (Figure 2, Table I). These exceptions were always associated with a distinct shortening of the first sinus cycle after an impulse conducted through the accessory pathway.

From the Istituto Pluridisciplinare di Clinica Medica, Cattedra di Malattie Cardiovascolari, Universitá di Messina, Italy, and the Department of Medicine, Baragwanath Hospital, and the University of the Witwatersrand, Johannesburg, South Africa. Manuscript received March 3, 1986; revised manuscript received and accepted November 12, 1987.

TABLE I Analysis of the Number of Normal Beats Intervening Between Two Consecutive Preexcitation Beats

Number of normal intervening beats	0	1	2	3	4	5	6	7	8	9	10
Frequency	0	5	55	0	1	9	0	0	10	0	2

In the case presented here, the preexcitation beats occur according to a pattern that could be defined as a trigeminal or a concealed trigeminal distribution. Schamroth and Marriott[2] noted that in the presence of a seemingly haphazard distribution of ventricular extrasystoles, the manifestation of intervening sinus beats in numbers that conform to the formula of $3n - 1$ (2, 5, 8, 11 and so forth) reveals a regular ectopic discharge; the ectopic focus discharges after every 2 sinus impulses. Some of the ectopic depolarizations, however, are not manifest because they are confined to the ectopic focus. On an analogous basis, the occurrence of preexcitation beats that are separated by normal beats in numbers of 2, 5 or 8 (apart from the exceptions to be discussed separately) suggests the presence of a regular 3:1 block within the accessory pathway. The distribution pattern of the intervening normal beats that

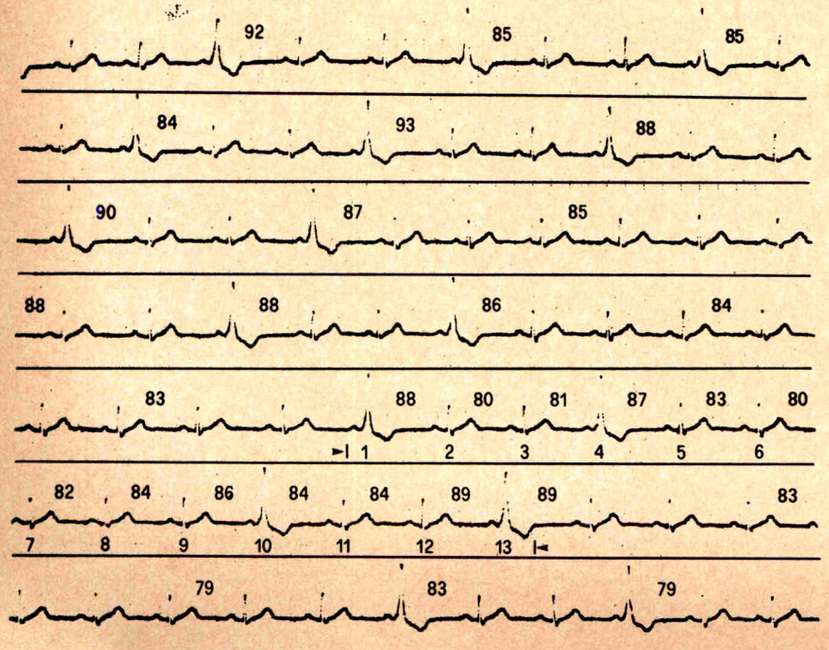

FIGURE 1. Electrocardiogram: continuous recording of standard lead I. The section between the arrows is diagrammed in Figure 3. Numbers above the tracing express the PP intervals in hundredths of a second. Numbers below the tracing label the beats that are diagramatically represented in Figure 3.

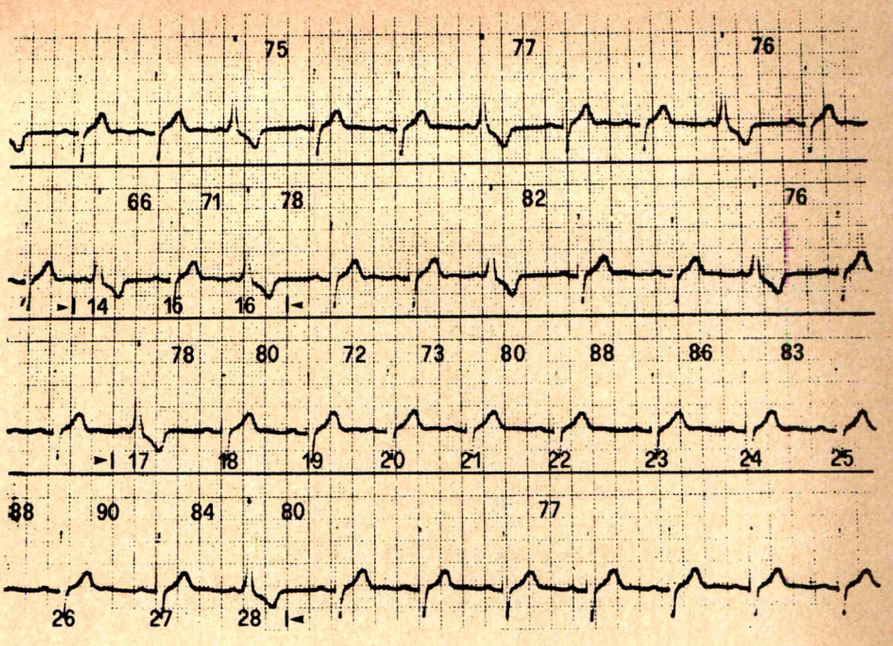

FIGURE 2. Electrocardiogram: continuous recording of lead V_6. Symbols as in Figure 1.

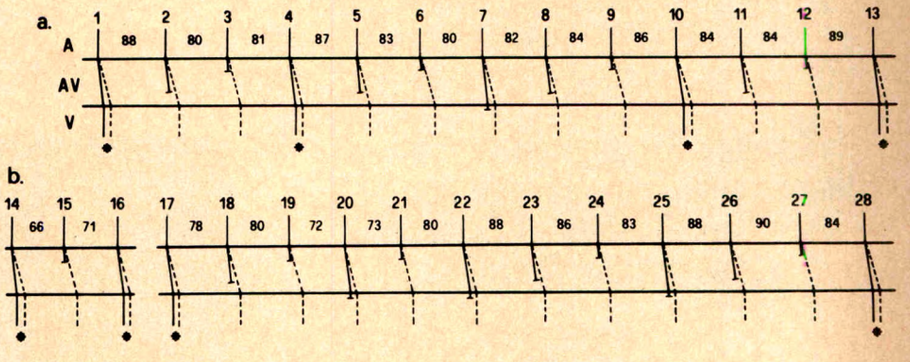

FIGURE 3. Ladder diagram illustrating atrioventricular conduction of sinus impulses. Conduction through the atrioventricular node and the His bundle is reflected by the *dashed lines*. *Solid lines* represent conduction through a Kent bundle. The sinus impulses are labeled with progressive numbers. The preexcitation complexes are labeled with asterisks. PP intervals are expressed in hundredths of a second. *A* and *B* refer to Figures 1 and 2, respectively. See text.

conform to the formula of $3n - 1$ suggests that 3:1 block regularly occurs in the accessory pathway, with some of the impulses penetrating the accessory bundle, but not reaching the ventricles.

The analysis of this phenomenon is shown in Figure 3A. All the sinus impulses are regularly conducted by the normal atrioventricular pathway, as reflected by the dashed lines; conduction through the Kent bundle is represented by the solid lines. The term "conduction" will hereafter only be applied to anterograde conduction of the impulse through the accessory pathway. Impulse 1 is conducted, resulting in a preexcitation complex. Impulses 2 and 3 are blocked. Impulse 2, however, penetrates deeply into the accessory pathway, undergoing a distal block, while impulse 3 is blocked in a proximal zone of the accessory pathway. The deep penetration of impulse 2 is thus responsible for the block of impulse 3. The proximal block of impulse 3 enables impulse 4 to be conducted as would occur after the block of a classic Wenckebach sequence. Thereafter, impulse 4 is conducted in a similar manner to impulse 1; and impulses 5 and 6 are conducted like impulses 2 and 3. The first 4 beats of the diagram thus represent 3:1 Kent bundle conduction. If this pattern is continuous, impulse 7 would be expected to be conducted. It does not do so, however, and the next preexcitation beat is associated with impulse 10. Thus, the 2 preexcitation beats associated with impulses 4 and 10 are separated by 5 intervening normal beats. And if impulse 10 did not result in preexcitation, the next preexcitation beat would be associated with impulse 13, so that 8 intervening normal beats would manifest. Thus, impulses number 1, 4, 7, 10 and so forth are actually conducted through the accessory pathway. Some of them, however, do not result in preexcitation, probably due to block at ventricular level as a consequence of a "mismatch impedance." In other words, the sinus impulse traverses the Kent bundle and reaches the ventricle, but the impulse conducted by the thin accessory pathway constitutes too weak an electrical signal for it to be propagated to the relatively large ventricular mass.[3-5] The presence of anterograde

concealed conduction in the accessory pathway is thus suggested by the occurrence of preexcitation beats in trigeminal or concealed trigeminal distribution.

On the other hand, there is no data supporting the presence of retrograde concealed conduction into the Kent bundle, namely the retrograde penetration of the accessory pathway by sinus impulses conducted through the His bundle.

The exceptions to the formula of concealed trigeminal Kent bundle conduction are shown in Figure 3B. These exceptions only occur when the PP interval after a conducted impulse is distinctly short. Thus beat 14—a preexcitation complex—is followed by a PP interval of 0.66 second. As a result, impulse 15 cannot penetrate deeply into the Kent bundle, as occurs after a longer PP interval, but it is blocked in a proximal zone of the accessory pathway. This enables impulse 16 to be conducted through the accessory pathway, giving rise to a preexcitation complex. The lack of penetration of impulse 15 explains the apparent paradoxic improvement of the conduction ratio with an increase in sinus rate, that is, the change from 3:1 to 2:1 accessory pathway conduction.

A further manifestation of this phenomenon is also shown in Figure 3B. This illustrates 10 normal beats that intervene between successive preexcitation complexes. Impulse 17 results in preexcitation, while impulses 18 and 19 are blocked. Impulse 20, which can be potentially conducted by the accessory pathway to the ventricles, is, however, associated with a normal beat. This lack of ventricular preexcitation is due to mismatch impedance. Impulse 21, then, reaches the Kent bundle after a critically short PP interval, and suffers a proximal block. Impulse 22 is thus conducted, but does not result in preexcitation for the same reason associated with impulse 20. The next preexcitation beat is associated with impulse 28. As with the preceding example, the exception to the formula $3n - 1$ is due to the inordinately short PP interval after impulse 20. This exception occurred when a PP interval after a *conducted* beat was <0.74 second. Shorter PP intervals that follow *nonconducted* impulses do not affect the regular trigeminal or concealed trigeminal pattern of the preexcitation.

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Cardiac Strangulation: Two-Dimensional Echo Recognition of a Rare Complication of Epicardial Pacemaker Therapy

JOEL I. BRENNER, MD
SHARON GAINES, MD
JOYCE CORDIER, RDMS
BRUCE I. REINER, MD
PHILLIP J. HANEY, MD
STEVEN R. GUNDRY, MD

Permanent epicardial pacemaker therapy is occasionally required in newborn infants for congenital complete heart block and in young infants for surgically acquired heart block.[1,2] In addition to the usual concerns encountered in any age group, such as lead fracture, pacemaker dysfunction, pericardial effusion and infection,[3-5] infants present the additional problem of requiring an adequate length of wire to allow for growth. We report an unusual complication of pacemaker therapy in a newborn: cardiac strangulation.

From the Departments of Pediatrics, Radiology and Surgery, the University of Maryland School of Medicine—UMH, 22 South Greene Street, Baltimore Maryland. Manuscript received October 30, 1987; revised manuscript received and accepted November 13, 1987.

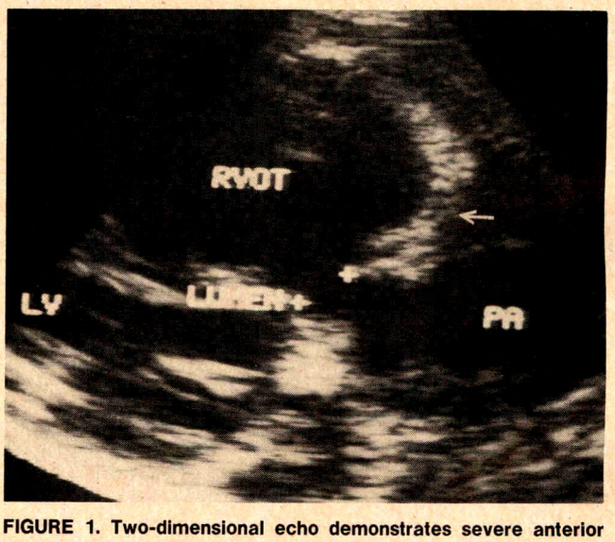

FIGURE 1. Two-dimensional echo demonstrates severe anterior compression of the right ventricular outflow (RVOT) by the pacemaker wire (*arrow*), with only the posterior lumen providing connection to the pulmonary artery (PA). Massive enlargement of the RVOT and compression of the left ventricle (LV) is also noted.

A.B. initially presented 8 weeks before delivery for evaluation of fetal bradycardia, caused by complete atrioventricular block. The atrial rate was 140 beats/min, while the ventricular rate varied between 40 and 50 beats/min. A structurally normal heart with biventricular dilatation was noted in utero. No pleural or pericardial effusion was demonstrated. The pregnan-

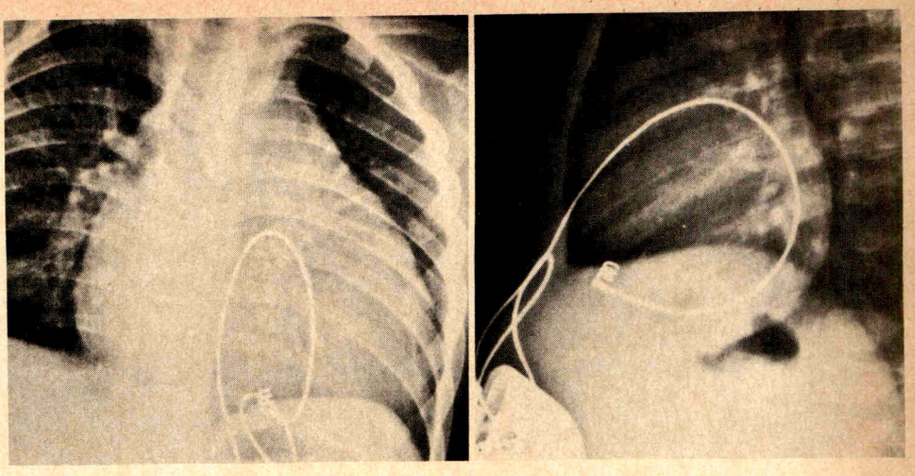

FIGURE 2. Anterior-posterior and lateral chest x-ray showing pacemaker wire encircling the heart.

cy terminated at 36 weeks by spontaneous delivery of a 2.8 kg infant with ventricular rates in the 40 beats/min range and clinical evidence of congestive heart failure and poor perfusion. Temporary endocardial pacemaker therapy was performed and the baby stabilized. At 6 days of age a permanent epicardial pacemaker was placed in a subcutaneous pocket in the left upper quadrant of the abdomen and a permanent screw-in epicardial electrode was inserted onto the diaphragmatic surface of the right ventricle. A loop of pacemaker wire was left in the anterior pericardium as well as in the abdominal cavity. Symptoms of congestive heart failure resolved after permanent pacing, and normal growth and development ensued. Cardiac evaluations during 15 months of follow-up were unremarkable except for paced ventricular rhythm, which gradually decreased to 69 beats/min.

At 20 months of age the child was brought to the emergency room with a 3-day history of frequent falling, intermittent pain in the right arm and syncope. At the time of examination he was in no distress. The heart rate was 69 beats/min, and an electrocardiogram demonstrated a paced ventricular rhythm. Cardiac examination was pertinent for a grade III/VI, harsh ejection systolic murmur along the left sternal edge. The liver was palpable 6 cm below the right costal margin, but the peripheral pulses and perfusion appeared normal.

Echocardiography demonstrated a structurally normal heart, with the new finding of massive right atrial and ventricular dilatation. Severe compression of the anterior right ventricular outflow tract (Figure 1) and the posterior left ventricular free wall was noted. Doppler interrogation of the pulmonary artery indicated a peak pressure difference across the right ventricular outflow tract of 80 to 100 mm Hg; color flow study demonstrated a 6-mm posterior lumen in the right ventricle-pulmonary artery connection. Chest x-ray showed the pacing wire encircling the heart (Figure 2). Emergency surgery performed that day confirmed the strangulation of the heart. The pacemaker wire had carved a deep trough in the atrioventricular groove that compressed the right coronary artery, main pulmonary artery (Figure 3), left main coronary artery and left atrium, and encircled the posterior LV wall. The pacing wire was dissected out of its fibrous sheath, brought around the heart and placed below the diaphragm. The patient was discharged the second postoperative week.

Symptoms of dizziness or syncope in a pacemaker-dependent patient should lead to immediate investigation of pacemaker function. In this patient, a dramatic change on physical examination, with evidence of right ventricular hypertension and systemic venous congestion, required additional explanation. Two-dimensional echocardiography and Doppler facilitated the definitive diagnosis of cardiac strangulation by

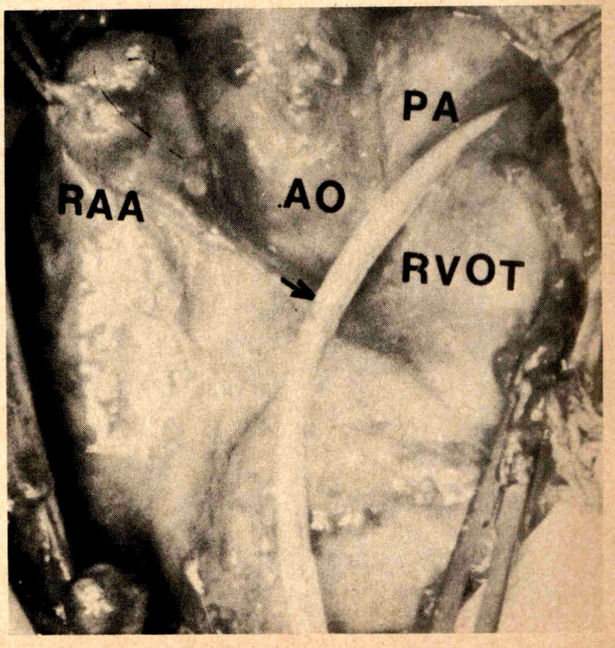

FIGURE 3. Intraoperative photo, confirming compression of right ventricular outflow (RVOT) by pacemaker wire (*arrow*) creating a deep groove as it courses posteriorly. AO = ascending aorta; PA = pulmonary artery; RAA = right atrial appendage.

an epicardial pacemaker electrode. The intermittent complaints of arm pain were likely related to myocardial ischemia from coronary arterial compression, confirmed at the time of surgery. Although the loop of pacemaker electrode was left in the anterior pericardial space, traction, cardiac motion and patient growth resulted in cardiac entrapment with potentially disastrous results.

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Incessant Pacemaker Vario® Operation

THOMAS M. CUNNINGHAM, MD

The Vario® function is a feature of certain pacemakers that allows noninvasive voltage threshold determinations.[1] After programming the Vario option, magnet application over the pulse generator results in 16 asynchronous impulses at a frequency of 99/min (new unit), followed by 15 asynchronous impulses at a frequency of 120/min. A stepwise decrease in amplitude occurs during these latter 15 cycles, followed by a final 0 volt output signal. The decrement in voltage per cycle is determined by the programmed amplitude as well as battery status. In a new unit, at a 5 volt output, the step differential is 0.32 volts. Initiation of the Vario test results from engagement of a reed switch by the test magnet. A case is described where failure of the reed switch to disengage after magnet removal led to continuous Vario cycling.

From Palm Drive Hospital, Sebastopol, California. Manuscript received April 20, 1987; revised manuscript received and accepted November 2, 1987.

A 77-year-old man underwent implantation of a Telectronics 255 bipolar VVI pacemaker for atrial fibrillation with complete heart block. Routine pacemaker follow-up 6 months later included noninvasive threshold testing by the Vario technique. After determining a threshold of 1.8 volts (at 0.25-ms pulse duration), the magnet was removed. Despite magnet withdrawal and attempts to program out of the Vario mode, the cyclic pattern persisted, including asystolic pauses from the first subthreshold output pulse until resumption of magnet test rate pacing at 99/min (Figure 1). Other parameters, such as amplitude and pulse width, were likewise unaffected by attempts at reprogramming. The patient was asymptomatic during the asystolic periods, although facial pallor was evident, followed by facial hyperemia during pacing. Surgery was promptly performed, with replacement of the pulse generator. During surgery, manipulation of the original unit in the pocket resulted in cessation of Vario cycling and return of normal pacemaker functioning. A defective reed switch was discovered at the

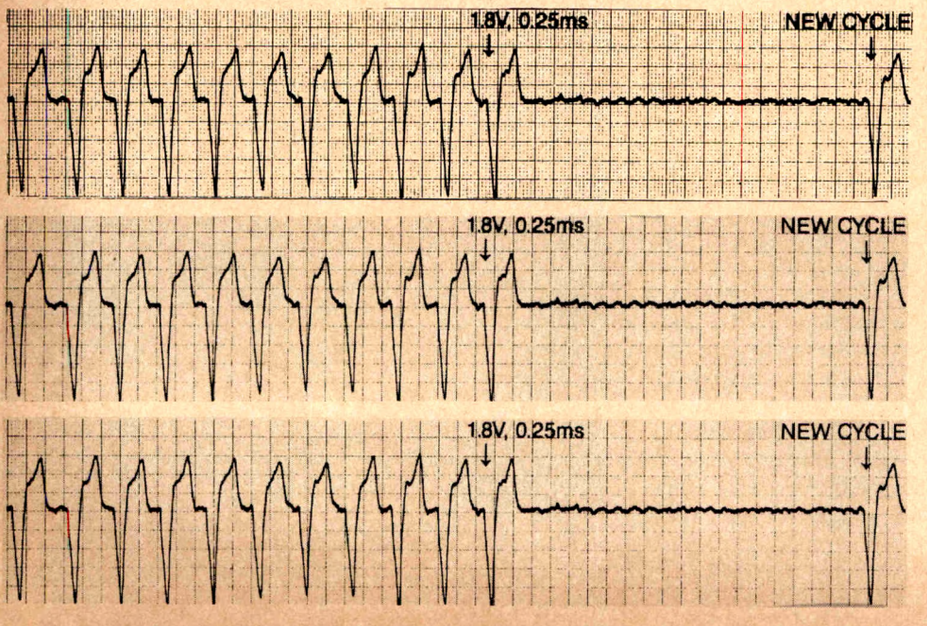

FIGURE 1. Continuous Vario operation, including asystolic pauses, after removal of the test magnet.

time of analysis of the pulse generator (personal communication, Telectronics, Inc.).

Noninvasive threshold determinations are useful in assuring an adequate margin of safety for pacemaker operation, especially when output is reduced to maximize generator longevity. The Vario technique is both easily performed and precise. This report illustrates a possible complication to this method, related to reed switch malfunction, with continuous Vario cycling. In patients in whom pacemaker dependency is present and the threshold is high, dangerously long pauses could result.

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Modulation of Atrioventricular Nodal Conduction Using Radiofrequency Current

KLAUS-PETER KUNZE, MD
MICHAEL SCHLÜTER, PhD
MANFRED GEIGER, MD
KARL-HEINZ KUCK, MD

Transvenous catheter ablation of the atrioventricular (AV) node has become a new therapeutic alternative in the treatment of patients with drug-resistant supraventricular tachycardia. After high-energy direct current shocks are delivered to the AV junction, conduction block is achieved in about 80% of patients, with subsequent control of symptoms. Pacemaker implantation, however, is mandatory because no, or only slow, junctional or ventricular escape rhythms emerge after ablation.[1] Therapeutic means currently under investigation for the modification of AV nodal conduction are transcatheter application of radiofrequency current[2] or laser energy.[3] We report the successful modulation of AV nodal conduction by radiofrequency current in a patient with intermittent, medically refractory atrial fibrillation.

A 69-year-old woman was referred to our hospital because of intermittent atrial fibrillation associated with rapid ventricular rates leading to presyncopal attacks. She had been treated unsuccessfully with 7 antiarrhythmic drugs, including amiodarone. The physical examination showed no abnormal findings. Routine laboratory tests, 2-dimensional echocardiogram and chest x-ray all had normal results. The 12-lead electrocardiogram revealed regular sinus rhythm with normal conduction intervals and normal ST segments. Twenty-four hour long-term electrocardiography disclosed that sinus rhythm was frequently interrupted by episodes of atrial fibrillation with ventricular rates of up to 190 beats/min.

After informed written consent had been obtained, the patient underwent an attempt to impair AV nodal conduction by application of radiofrequency current. Standard 6Fr quadripolar USCI electrode catheters were positioned under fluoroscopic control in the high right atrium and the right ventricular apex. An 8Fr bipolar electrode catheter that served for radiofrequency current application was placed at the region of the AV node. A 5Fr arterial cannula allowed continuous measurement of arterial blood pressure. After positioning of the catheters a bolus of 100 U/kg body weight of heparin was given intravenously, followed by infusion of 1,000 U/hour for the next 12 hours. Stimulation was performed with an ERA-S-His stimulator (Biotronik GmbH).

A custom-built radiofrequency generator delivered 300-kHz electrical energy at a constant preset voltage for a variable preset time. The unit allows continuous registration of delivered current and voltage, and, thus, calculation of tissue impedance and delivered power and energy. Six surface electrocardiographic leads, 4 endocardial leads, arterial blood pressure and delivered current and voltage were registered simul-

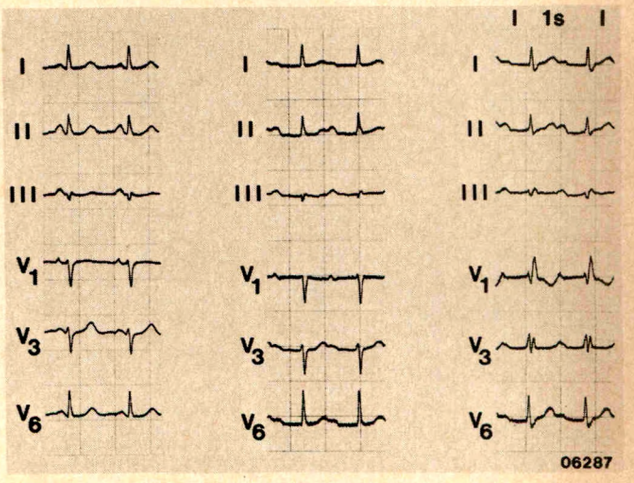

FIGURE 1. Six-lead surface electrocardiograms before radiofrequency application (*left*), after the sixth application (*middle*) and 30 minutes after the last application (*right*). Before radiofrequency application the sinus cycle length was 680 ms and the PQ, QRS and QT intervals were within normal limits. The electrocardiograms after the sixth application and 30 minutes after the last application show a marked prolongation of the PQ interval to 340 ms. Right bundle branch block at the end of the procedure was inadvertently induced by the seventh radiofrequency pulse.

From the Department of Cardiology, University Hospital Eppendorf, Hamburg, Federal Republic of Germany. This work was supported by a grant from the Dr. Werner-Otto-Stiftung, Hamburg, Federal Republic of Germany. Manuscript received August 14, 1987; revised manuscript received November 5, 1987, and accepted November 6.

taneously at a paper speed of 100 mm/s (stimulation study) or 25 mm/s (during radiofrequency application) on a 16-channel recorder (Siemens-Mingograph).

Initially, the anterograde effective refractory period of the AV node and the Wenckebach cycle length were determined (295 ms and 280 ms, respectively). During rapid atrial stimulation for determination of the Wenckebach cycle length, sustained atrial fibrillation with a ventricular rate of 190 beats/min was induced and associated with dizziness and angina. External cardioversion reestablished a stable sinus rhythm, and the ablation procedure was begun. The 8Fr catheter was positioned such that its distal electrode recorded the largest possible atrial potential but also a small His bundle potential. Then a total of 9 radiofrequency pulses of various power and duration were introduced between the catheter tip and a back paddle. After each pulse the AH and PQ intervals and the anterograde AV nodal effective refractory period were determined. With the initial 2 pulses, a power of 13.8 to 14.4 watts was applied for 20 seconds. This did not show a significant effect on AV nodal conduction and refractoriness. With the next 4 pulses, 31 to 34 watts were delivered for 20 seconds, resulting in a marked prolongation of the AH and PQ intervals but only a minor increase of the anterograde AV nodal effective refractory period. We proceeded with 3 pulses of the same power, each lasting 30 seconds. The seventh pulse inadvertently caused right bundle branch block, and the catheter had to be relocated. The subsequent 2 pulses significantly increased the anterograde AV nodal effective refractory period.

After the ninth radiofrequency, third-degree AV nodal block occurred for 22 seconds, but then 1:1 AV nodal conduction resumed. After another 30 minutes the AH interval during sinus rhythm (660 ms cycle length), which had been 60 ms before radiofrequency application, had increased to 240 ms. The PQ interval had increased from 125 to 325 ms and the width of the QRS complex had also increased from 90 to 140 ms, because of the creation of a right bundle branch block.

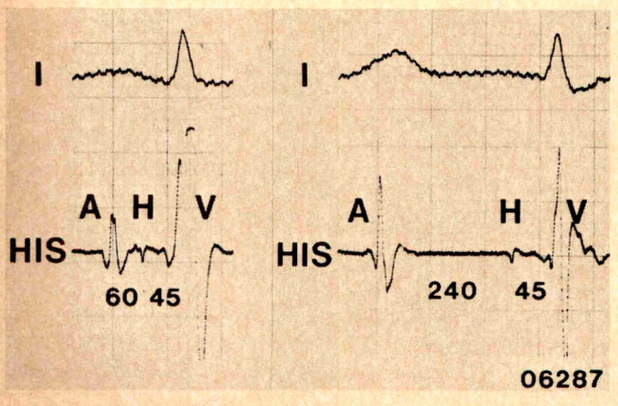

FIGURE 2. Surface electrocardiogram (lead I) and His bundle recording before radiofrequency application (*left*) and 30 minutes after the last application (*right*). Note the marked increase of the PQ interval caused by prolongation of the AH interval from 60 to 240 ms. A = atrial potential; H = His bundle potential; HIS = His bundle electrogram; V = ventricular potential.

The QT interval and the HV interval remained unchanged at 355 and 45 ms, respectively (Figures 1 and 2). Anterograde AV nodal effective refractory period and Wenckebach cycle length also increased (415 and 405 ms, respectively).

At the end of the procedure atrial fibrillation was induced by high right atrial stimulation. The ventricular rates now ranged from 75 to 135 beats/min. Because of the marked prolongation of the PQ and AH intervals during sinus rhythm and the slower ventricular rates during atrial fibrillation the procedure was terminated at this point. It was assumed that the impairment of AV nodal conduction by radiofrequency energy was sufficient to alleviate the patient's symptoms. She was referred to the intensive care unit where cardiac rhythm was monitored for another 48 hours. Atrial fibrillation was continuously present during this time, with maximal ventricular rates of 140 beats/min.

Delivery of radiofrequency energy was painless and could be performed without general anesthesia.

At the first clinical follow-up visit 1 month after AV nodal modulation, the patient was asymptomatic without antiarrhythmic medication. The 12-lead electrocardiogram showed a regular sinus rhythm with first-degree AV nodal block and complete right bundle branch block. During 24-hour long-term electrocardiography several episodes of intermittent atrial fibrillation, lasting for up to 30 minutes with maximal ventricular rates of 135 beats/min, occurred but the patient remained asymptomatic. On 2-dimensional echocardiography there was neither evidence of functional impairment of the ventricles nor right atrial thrombus formation. Laboratory tests showed no abnormal findings. The patient took oral acetylsalicylic acid for another 2 months.[4]

This report describes the successful modulation of AV nodal conduction by radiofrequency current in man. Prolongation of AV nodal refractoriness by radiofrequency application to the AV node led to marked symptomatic improvement in a patient with intermittent, drug-refractory atrial fibrillation and rapid ventricular response. Because this procedure resulted in first-degree AV nodal block without any evidence of progression to higher degrees of conduction block, no pacemaker was implanted.

The application of radiofrequency energy may prove to be a suitable and safe therapeutic measure for modulation of AV nodal conduction in patients with medically intractable supraventricular arrhythmias. The reproducibility of creating partial AV nodal block by radiofrequency current needs to be established in a larger patient population.

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CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. It has been reported that LOPID may increase levels of high density lipoprotein (HDL) subfractions, HDL_2 and HDL_3 as well as apolipoproteins AI and AII. Epidemiological studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease. It is not yet known whether pharmacological interventions designed to raise HDL-cholesterol alter morbidity or mortality due to coronary heart disease.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID inhibits synthesis and increases clearance of VLDL carrier apolipoprotein B, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, mostly as the glucuronide conjugate, with less than 2% excreted as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO: HDL Cholesterol / Total Cholesterol
		Total	VLDL	LDL	HDL	
IIa	−44%	−4.2%	−44.3%	−5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	−6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. The initial treatment for hyperlipidemia is dietary therapy specific for the type of hyperlipoproteinemia. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV or type V hyperlipoproteinemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk. LOPID has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of gemfibrozil-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID (gemfibrozil capsules, USP) administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis – LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID (gemfibrozil capsules, USP) therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy** – Before instituting LOPID therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy** – Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Impairment of Fertility** – Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

4. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

5. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

6. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

7. **Liver Function** – Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

8. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID (gemfibrozil capsules, USP) therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria

Central Nervous System: headache, dizziness, blurred vision

Musculoskeletal: painful extremities

Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:

Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia

Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints, myositis

Central Nervous System: vertigo, insomnia, paresthesia, tinnitus

Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)

Miscellaneous: fatigue, malaise, syncope, alopecia

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

Caution – Federal law prohibits dispensing without prescription.

February 1987 0669G017

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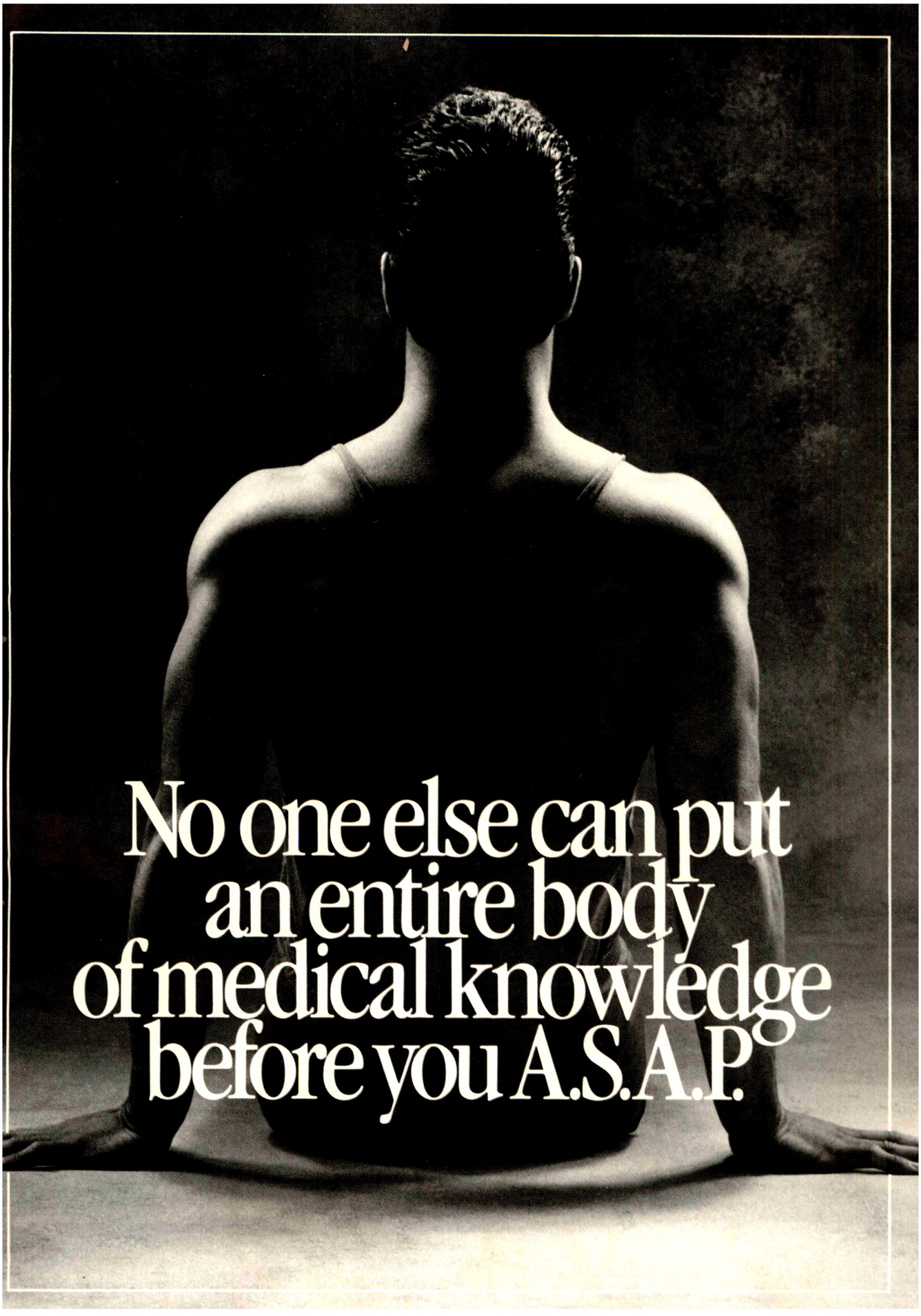
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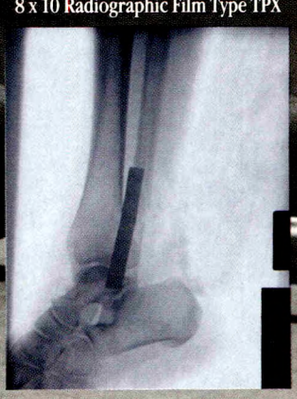

S.P.E.C.T. Brain Scan –
Colorgraph Type 691 Overhead Transparency Film

Ophthalmology Fundus Image
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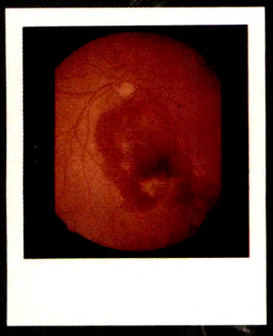
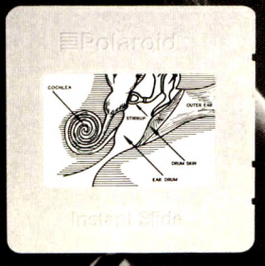
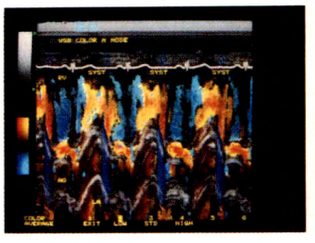


Medical Illustration –
PolaGraph 35mm Instant Film

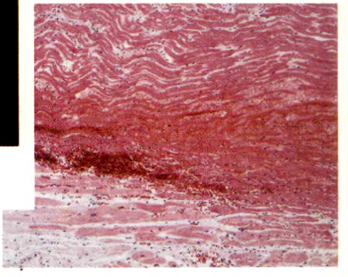


Hemangioma – Polacolor
ER Type 669 Film

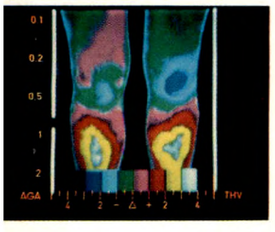
Color M-Mode in a Ventricular
Septal Defect – AutoFilm Type 339



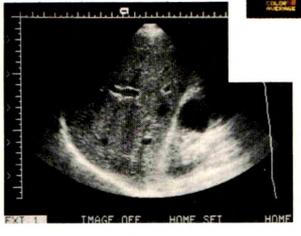
Microscopic Image of Myocardial
Infarction – Polacolor ER Type 59 Film



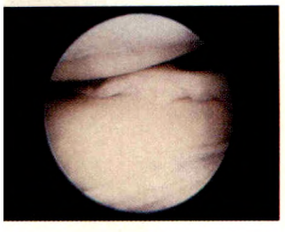
hermograph of Knee Inflammation –
Polacolor ER Type 669 Film



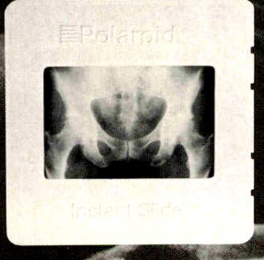
Abdominal Ultrasound
Showing Right Kidney –
AutoFilm Type 331



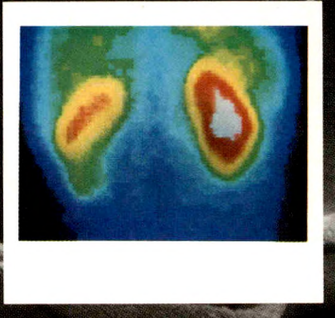
Arthroscope of Torn Meniscus –
AutoFilm Type 339



X-Ray of Pelvis –
PolaPan Instant 35mm Film



Scintigram of Kidneys –
AutoFilm Type 339



Nerve Injury Illustration –
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Result	Product	Format/Size	Speed ISO & DIN equivalents	Normal Development Time at 75°	Special Characteristics
Instant Color Prints	Type 779	Integral Pack 3 1/2x4 1/2 in.	ISO 640/29°	Self-timing	Balanced for daylight and electronic flash. Image visible in 10-15 seconds.
	Time Zero Type 778	Integral Pack 3 1/2x4 1/2 in.	ISO 150/23°	Self-timing	Balanced for daylight. Image visible in 10-15 seconds.
	Type 909	Integral Pack 4x4 in.	ISO 600/29°	Self-timing	Balanced for daylight and electronic flash.
	Type 339	Integral Pack 4.5x4.2 in.	ISO 640/29°	Self-timing	General purpose, high speed, medium contrast.
	Polacolor ER Type 669	Pack 3 1/4x4 1/2 in.	ISO 80/20°	60 seconds	Medium contrast; extended dynamic range. Balanced for daylight and electronic flash.
	Polacolor ER Type 809	Sheet 8x10 in.	ISO 80/20°	60 seconds	Medium contrast; extended dynamic range. Balanced for daylight and electronic flash.
	Polacolor ER Type 59	Sheet 4x5 in.	ISO 80/20°	60 seconds	Medium contrast; extended dynamic range. Balanced for daylight and electronic flash.
Instant B&W Prints	Type 331	Integral Pack 4.5x4.2 in.	ISO 200/24°	Self-timing	Extended dynamic range.
	Type 084	Pack 3 1/4x4 1/4 in.	ISO 3000/36°	15 seconds	For cathode ray tube recording.
	Type 667	Pack 3 1/4x4 1/4 in.	ISO 3000/36°	30 seconds	General purpose, high speed film. No coating required.
	Type 611	Pack 3 1/4x4 1/4 in.	ISO 200/24°	45 seconds	Low contrast. Extended dynamic range and exposure latitude. For video image recording.
	Type 803	Sheet 8x10 in.	ISO 800/30°	30 seconds	Fine grain medium contrast film. No coating required.
Instant Color Overhead Transparency	Colorgraph Type 691	Pack 3 1/4x4 1/4 in.	ISO 80/20°	4 minutes	Small format overhead projection use.
	Colorgraph Type 891	Sheet 8x10 in.	ISO 80/20°	4 minutes	For overhead projection use.
Instant B&W Radiographic Transparency	Type TPX	Sheet 8x10 in.	N/A	60 seconds	Medium to high contrast. High speed Orthochromatic sensitivity. No darkroom needed.
Instant 35mm Color Slides	PolaChrome CS	35mm Roll (12 & 36 Exposures)	ISO 40/17°	60 seconds	General purpose, continuous tone color.
	High Contrast PolaChrome	35mm Roll (12 Exposures)	ISO 40/17°	2 minutes	High contrast color for text and graphic imaging.
	PolaBlue BN	35mm Roll (12 Exposures)	ISO 4/7° (Tungsten) ISO 8/10° (Electronic Flash)	4 minutes	White-on-blue negative film for word slides, charts and graphs.
Instant 35mm B&W Slides	PolaPan CT	35mm Roll (12 & 36 Exposures)	ISO 125/22°	60 seconds	General purpose, continuous tone black and white.
	PolaGraph HC	35mm Roll (12 Exposures)	ISO 400/27°	2 minutes	High contrast black and white. Ideal for line copy.

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Sudden Death and Cardiomegaly Unassociated with Coronary, Valvular, Congenital or Specific Myocardial Disease

AMY H. KRAGEL, MD
WILLIAM C. ROBERTS, MD

Sudden death has many causes and necropsy usually allows delineation of the specific cause.[1] During the past 8 years we have studied at necropsy 6 patients, all men, who died suddenly outside the hospital and although necropsy disclosed cardiomegaly, a specific cause of death was not discernible. Certain clinical and morphologic features in these 6 patients are described in this report.

All 6 patients (Table I) died outside the hospital and the necropsy in each was performed at the District of Columbia Medical Examiner's Office. In each case the heart was examined initially by one (WCR) of us, subsequently brought to the National Institutes of Health, and later examined by both of us. After accurately weighing the heart, the epicardial coronary arteries were incised transversely to their longitudinal axes at 5-mm intervals. At least 2 sections of left ventricular wall extending from endocardium to epicardium and measuring at least 2 cm in length were processed for histologic study and examined. The records of the Medical Examiner's Office also were examined. The records indicated that only 1 patient (no. 4, Table I) had been hospitalized previously and that a year before death for therapy of systemic hypertension.

The 6 men, all black, ranged in age from 41 to 68 years (mean 49). Three (numbers 4 through 6, Table I) had historic evidence of "high blood pressure" in the past and 1 (no. 4) took an antihypertensive medicine (diuretic). Two patients (numbers 4 and 6) also were known to have received digitalis therapy; patient 4 had had a single episode of pulmonary edema, which was thought to be secondary to severe systemic hypertension, about 1 year before death. No evidence of congestive heart failure was present in the other 4 patients. Two patients (numbers 3 and 4) were known to be habitual alcoholics. None were known cocaine or opiate addicts. The circumstances of death were the following: 4 patients (numbers 1 through 4) were found dead after having been seen alive and well within the previous 6 hours; the other 2 died instantaneously or nearly so (while in a coffee shop during a work break [no. 5]; after his first seizure while walking on the sidewalk [no. 6]).

Toxicologic studies (including screening tests performed on blood, bile and lung tissue for over 300 drugs including volatile alcohols, narcotics, antihistamines, phenothiazines, barbiturates, synthetic narcotics, various sedatives and cocaine) were performed at necropsy in 5 patients: in 4 patients results of all studies were negative; in 1 patient (no. 1) the blood alcohol level was 50 mg/dl (>100 mg/dl is legally intoxicated). The weight of the heart ranged from 440 to 700 g (mean 569). Body weight ranged from 63 to 104 kg (mean 87). Heart weight as a percent of body weight ranged from 0.51 to 0.98 (mean 0.69) (normal 0.42 to 0.46). Their height ranged from 165 to 193 cm (mean 178). The epicardial surface was smooth in each case. The subepicardial adipose tissue was increased in 5 patients. The coronary arteries arose and coursed normally in all 6 patients. The sizes of the coronary ostia appeared normal in all 6 patients. In 4 patients the right coronary artery was dominant; in 1 patient, the left circumflex artery was dominant and in 1 patient both right and left circumflex arteries coursed to the crux (codominant). The lumens of the epicardial coronary arteries were completely or virtually devoid of atherosclerotic plaques or other material. The 4 valves in each patient were normal or virtually normal. No foci of grossly visible myocardial fibrosis or necrosis or other lesions were present in any heart. Both atrial and ventricular septa were intact in all 6 patients. No intracardiac thrombi or mural endocardial plaques were present in any of the 4 cardiac chambers in any of the 6 patients.

The liver ranged in weight from 1,810 to 2,660 g (mean 2,303). No patient had evidence of hepatic cirrhosis. The spleen ranged in weight from 140 to 390 g (mean 222) and all appeared normal upon gross inspection. No grossly visible lesions were found in the lungs in any patient. The brain grossly appeared normal in 5 patients; in 1 (no. 4), 3 small healed cortical infarcts were observed. The kidneys appeared normal in 4 patients and in 2 patients (numbers 5 and 6) showed changes most compatible with those secondary to systemic hypertension. Patient no. 3 had changes of chronic pancreatitis. The ascending aorta was normal in 5 patients and in 1 (no. 3) large atherosclerotic plaques were present focally in the tubular portion of ascending aorta. The latter patient's coronary arteries, in contrast, were virtually free of atheroslcerotic plaques.

Sections of myocardium showed variable degrees of myocyte hypertrophy and interstitial fibrosis. There were no foci of myocardial necrosis or large

TABLE I Certain Findings in the 6 Men

Pt No.	Age (yrs)	Body Weight (kg)	Height (cm)	Heart Weight (g)	Heart Weight as Percent of Body Weight	Dilatation (0 to 3+) RV	LV
1	41	104	185	680	0.65	0	0
2	44	84	178	440	0.51	0	0
3	45	63	168	515	0.61	0	0
4	46	97	180	620	0.98	1+	2+
5	50	73	165	460	0.63	0	0
6	68	92	193	700	0.76	2+	2+

LV = left ventricle; RV = right ventricle.

From the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.
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areas of replacement fibrosis or presence of inflammatory cells or other abnormal infiltrates in the myocardial walls. No foci of myofiber disarray were observed in sections of ventricular septa. The intramural coronary arteries were normal.

The most likely cause for the cardiomegaly in our 6 patients is systemic hypertension. Systemic arterial pressure was available in only 3 of the 6 patients and in each it was stated to have been elevated. None of the 6 patients had narrowing of any epicardial coronary artery, none had anatomic evidence of valvular, myocardial, congenital or pericardial heart disease. None had a coronary arterial anomaly. Cases of morbid obesity (>250 pounds) were excluded from this study.[2] Although it is well recognized that patients with systemic hypertension have an increased frequency of both atrial and ventricular arrhythmias compared with normotensive persons and that hypertensive persons with left ventricular hypertrophy have a higher frequency of these arrhythmias compared with hypertensive persons without left ventricular hypertrophy,[3,4] the occurrence of sudden death in persons with systemic hypertension in the absence of significant narrowing of 1 or more epicardial coronary arteries has not been described previously to our knowledge.

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Percutaneous Double Balloon Valvotomy for Rheumatic Tricuspid Stenosis

PAULO A. RIBEIRO, MD
MUAYED AL ZAIBAG, MRCP
SAAD AL KASAB, MRCP
MOHAMED IDRIS, MRCP
MURTADA HALIM, MRCP
MOHEEB ABDULLAH, MRCP
MAIE SHAHED, MRCP

We attempted tricuspid balloon valvotomy in 4 selected consecutive symptomatic patients (2 male and 2 female) (mean age 41 years), with severe tricuspid stenosis (TS) and mild mitral valve disease. The immediate and short-term results are reported. To define the physiologic effects of balloon tricuspid valvotomy, we studied the cardiac output of these patients at rest and during treadmill exercise, both before and after the procedure.

Written informed consent was obtained from all patients. Oral premedication was 10 mg of diazepam. Aortic pressure monitoring was achieved by inserting an 18-gauge cannula into the right femoral artery in patient 1 and by a 7Fr pigtail catheter inserted into the descending aorta in patients 2, 3 and 4. A 7Fr Berman angio catheter was passed from each femoral vein to measure the pressure gradient across the tricuspid valve and to perform a right ventricular angiogram before and after balloon inflation. After calibration and the recording of identical simultaneous right atrial pressure tracings from both catheters, one of them was advanced to the right ventricular cavity. To measure the gradient across the tricuspid valve, 10 consecutive cardiac cycles were recorded at a paper speed of 100 mm/s. The 0.038-inch Teflon-coated exchange guidewires (250 cm long) with preshaped curved tips were then advanced through two 7Fr pigtail catheters, which previously had been inserted percutaneously in each femoral vein; the end of each guidewire was positioned at the apex of the right ventricle (Figure 1). A 9Fr balloon catheter (Meditech), 15 to 20 mm diameter and 3 cm length, was advanced percutaneously over each guidewire and positioned across the tricuspid valve under fluoroscopic control in the 10° right anterior oblique projection; the correct position was confirmed by fluoroscopic detection of the indenta-

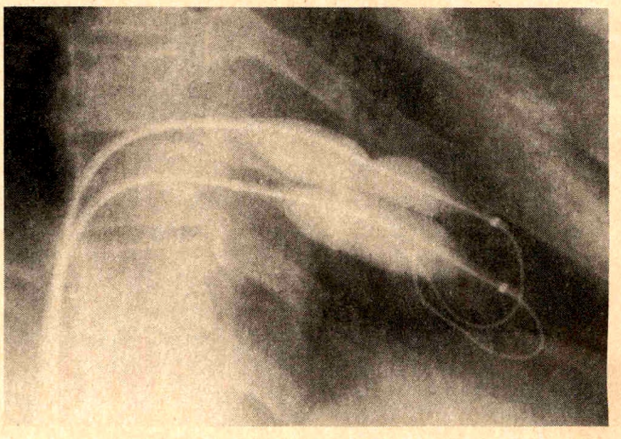

FIGURE 1. Two balloons positioned across the tricuspid valve. Note balloon indentation during early inflation in patient 3.

From the Military Hospital, PO Box 7897, Riyadh 11159, Kingdom of Saudi Arabia. Manuscript received September 14, 1987; revised manuscript received and accepted November 4, 1987.

TABLE I Hemodynamic and Angiographic Results Before (B) and After (A) Tricuspid Balloon Valvotomy

Pt No.		Tricuspid gradient (mm Hg)/Mean ED		TVA (cm^2)	HR (bpm)	Right Atrium Mean	Right Atrium A Wave	Right Atrium V Wave	TR	Balloon Size (mm)
1	B	6/4		0.9	64	8	17	9	0–1/4	15 + 15*
	A	2/0		2.0	68	4	10	4	0–1/4	15 + 20†
2	B	5/5		0.6	68	7	12	6	2/4	15 + 18*
	A	2/0		1.4	64	5	10	4	2/4	18 + 18†
3	B	5/7		0.7	102	6	—	9	3/4	18 + 20*
	A	2/2		1.4	104	4	—	6	3/4	
4	B	8/8		0.8	52	14	21	14	0–1/4	20 + 20*
	A	1/0		2.5	54	10	15	10	0–1/4	
Mean (± SD)	B	6.3 ± 1.4	6 ± 1.8	0.75 ± 0.1	72 ± 21	9 ± 4	17 ± 5	10 ± 3		
	A	1.9 ± 0.5‡	0.5 ± 1§	1.8 ± 0.5‡	73 ± 22‖	6 ± 3‡	8 ± 3‡	6 ± 3‡		

* first-choice balloons; † second-choice balloons.
‡ $p < 0.01$; § $p < 0.05$; ‖ difference not significant.
bpm = beats/min; ED = end-diastolic; HR = heart rate; SD = standard deviation; TR = tricuspid regurgitation by angiography; TVA = tricuspid valve area.

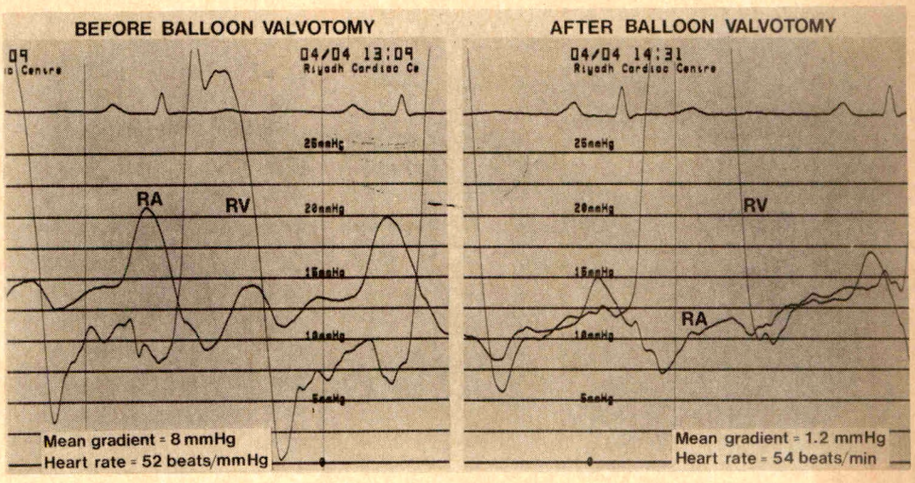

FIGURE 2. Right atrial (RA) right ventricular (RV) pressure gradient recording before and immediately after successful tricuspid balloon valvotomy in patient 4.

tion of the balloon during inflation. The balloons were inflated simultaneously to a maximum pressure of 5 atmospheres. A successful valvotomy was judged at the time by the loss of balloon indentation and confirmed by hemodynamic measurement (Figures 1 and 2). By these criteria, patients 1 and 2 required the use of larger sized balloons to achieve a successful result (Table I). The balloons were inflated for 8 to 12 seconds, and during this time the systolic arterial pressure remained above 80 mm Hg. The number of inflations ranged from 3 to 13 to achieve optimal balloon alignment across the stenotic tricuspid valve.

The study protocol included cardiac catheterization and 2-dimensional echocardiography, using a Hewlett Packard system, before the procedure, immediately after and again at 8- to 20-week follow-up. Treadmill exercise testing was performed in patients 2, 3 and 4, using a Marquette system, before valvotomy and at the 8- to 20-week follow-up. The cardiac output was measured at rest and 2 to 3 times during each stage of the exercise test by the thermodilution technique and measurements were repeated using the green dye method in patients 2 and 3, who had tricuspid regurgitation.

After tricuspid double balloon valvotomy the tricuspid valve area increased from 0.75 ± 0.1 to 1.8 ± 0.5 cm^2 ($p < 0.05$) (Table I). Angiographically there was no increase in the degree of tricuspid regurgitation in any of the 4 patients. Before balloon valvotomy, all 3 leaflets of the tricuspid valve were thickened, with restricted motion and diastolic doming. With real-time 2-dimensional echocardiography after valvotomy, doming persisted. There was some improvement in the motion of the anterior tricuspid leaflet in all 4 patients, of the posterior leaflet in 2 patients and of the septal leaflet in 1 patient (Figure 3). The 8- to 20-week follow-up hemodynamic studies showed a persistent 150% increase in tricuspid valve area to 1.9 ± 0.6 cm^2. There was a marked increase in resting cardiac output after tricuspid balloon valvotomy, from 2.5 ± 0.6 to 3.6 ± 1 liters/min ($p < 0.02$). At peak treadmill exercise there was an increase in cardiac output from 5.6 ± 1.4 to 7.4 ± 1.1 liters/min ($p < 0.01$) at similar heart rates. All patients reported symptomatic improvement, with

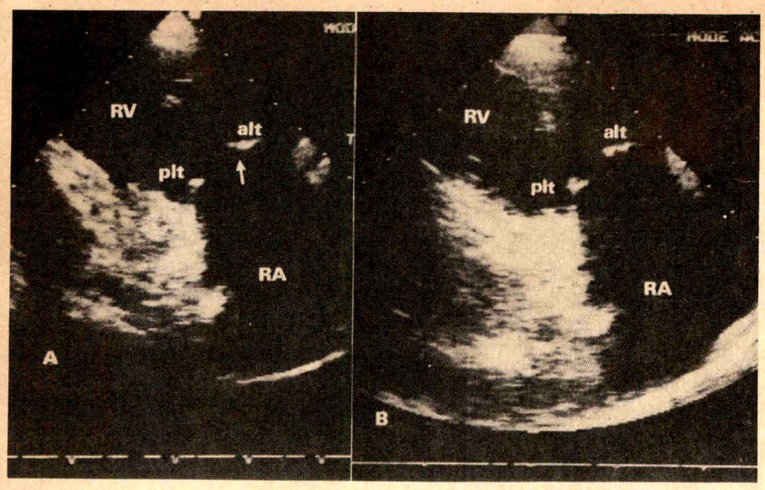

FIGURE 3. *A* and *B*. Parasternal right ventricular inflow view (diastolic frame). Note in tricuspid leaflet separation after successful balloon tricuspid valvotomy in patient 2. Alt = anterior leaflet of tricuspid valve; plt = posterior leaflet of tricuspid valve; RA = right atrium; RV = right ventricle.

virtual disappearance of fatigue and shortness of breath on exertion. The diastolic rumble disappeared in all 4 patients.

Our findings demonstrate unequivocally the feasibility of percutaneous double balloon tricuspid valvotomy for the relief of severe rheumatic TS. The 150% increase in tricuspid valve area after balloon valvotomy, together with the marked reduction in tricuspid valve gradients, persisted in short-term follow-up.

The major hemodynamic disturbance in TS is reduction in cardiac output.[1] In contrast to results of a mitral valve study,[2] we demonstrated that after tricuspid balloon valvotomy there was a significant increase in cardiac output both at rest and during treadmill exercise testing. These findings accord with the patients' symptomatic improvement.

Both this study and our initial case report[3] indicate that maximal tricuspid valve areas are achieved by balloon valvotomy with a 15 + 20, or 18 + 20 mm balloon combination, without inducing tricuspid regurgitation. We do not advocate balloon valvotomy in patients with significant tricuspid regurgitation; 2 of our patients (2 and 3) had angiographically moderate tricuspid regurgitation, although this was hemodynamically not significant as assessed by the mean right atrial pressure and V-wave amplitude (Table I).

The improvement in tricuspid valve area results achieved with our percutaneous double balloon valvotomy technique are comparable to those reported after surgical tricuspid valvotomy[4]; however, we had no morbidity or mortality. This technique is suitable not only in patients with pure severe TS but also for patients with concomitant severe rheumatic mitral and tricuspid stenosis.

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Clinical Features of Mitral Valve Prolapse Associated with Low Body Weight

RICHARD B. DEVEREUX, MD
ROGER CAPPUCCI, BS
RANDI KRAMER-FOX, MS

An association between mitral valve prolapse (MVP) and low body weight has been well documented in family,[1] general population,[2] and clinical[3] studies. The low body weight of patients with MVP may exert a clinically beneficial effect by permitting lower levels of blood pressure in MVP patients than in comparable control subjects.[1,4] The observation of a low prevalence of mitral clicks or murmurs in MVP patients, however, in 2 studies in which MVP was strongly associated with low body weight[2,5] has led some investigators to suggest that MVP in lean patients might represent a variant of normal devoid of the auscultatory features encountered in patients with clinically recognized MVP. To test this hypothesis, we related body habitus to auscultatory and other demographic and clinical features of MVP in consecutive adult family members documented to have MVP in a family study that has been previously reported in part.[1,6–7]

The 105 family members with MVP included 67 women and 38 men, aged 16 to 79 years (mean 36); 95

From the Department of Medicine, The New York Hospital-Cornell Medical Center, New York, New York. This study was supported in part by grant HL-22006 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received September 17, 1987; revised manuscript received October 22, 1987, and accepted October 25.

TABLE I Clinical Findings in Mitral Prolapse Subjects Grouped by Body Mass Index

	Group I (n = 35)	Group II (n = 35)	Group III (n = 35)
Body mass index (kg/m^2)	15.01–20.32	20.38–22.14	22.19–37.46
Age (yr)	30 ± 14‡	34 ± 15	44 ± 16‡
Female: No. (%)	27 (77)	23 (66)	17 (49)
Peak systolic blood pressure (mm Hg) (%)	118 ± 13*	122 ± 16	129 ± 22*
End-diastolic blood pressure (mm Hg) (%)	73 ± 6†	77 ± 9	80 ± 10†
Midsystolic precordial clicks (%)	9 (26)	9 (26)	13 (37)
Late systolic precordial murmurs (%)	5 (14)	5 (14)	2 (6)
Click and murmur (%)	10 (29)	5 (14)	2 (6)
Long/holosystolic murmur (%)	1 (3)	1 (3)	2 (6)
Any typical auscultatory feature (%)	25 (71)	20 (57)	19 (54)
"Silent" or midsystolic murmur (%)	10 (29)	15 (43)	16 (46)

Statistical significance, group I compared with group III: * $p < 0.02$; † $p < 0.005$; ‡ $p < 0.0005$.

were first-degree relatives of probands with clinically recognized MVP, 7 were second-degree relatives and 3 were spouses of probands or family members. MVP was diagnosed by M-mode and cross-sectional echocardiography using previously described criteria.[7] *Weight and height were recorded and used to calculate body mass index as the ratio of weight in kilograms/(height in meters).*[2] *Auscultation was performed in multiple positions and with isometric handgrip exercise by an investigator without knowledge of echocardiographic findings. Subjects were divided into 3 groups of 35 subjects each based on body mass index, with values of 15 to 20.3 kg/m^2 in group I, 20.4 to 22.1 kg/m^2 in group II and 22.2 to 37 kg/m^2 in group III. Statistical comparison between groups with lowest and highest body mass index was performed with unpaired Student t tests for continuous variables and the chi-square test, with Yates' continuity correction when appropriate for proportions. The statistical independence of relations between blood pressure and body mass index and age was assessed by stepwise multiple linear regression analysis.*

Demographic and clinical findings in the 3 groups are listed in Table I. Overall body mass index was below 22.7, the mean value corresponding to 1983 Metropolitan Life Insurance Co. ideal body weight,[8] *in 75 of 105 (71%) subjects with MVP. The group with lowest body mass index was disproportionately female (77%) compared with that with highest body mass index (49%) (chi-square = 6.47, $p < 0.02$), with an intermediate sex distribution in the middle tercile. Progressive increases in age and systolic and diastolic blood pressures occurred from the group with lowest to that with highest body mass index. Multiple linear regression analysis revealed highly significant ($p < 0.001$) correlations between age and systolic and diastolic pressures whereas independent correlations between body mass index and blood pressure levels approached but did not attain statistical significance.*

Midsystolic clicks occurred in isolation in 9 of 35 patients (26%) in the lower 2 terciles of body mass index and in 13 of 35 (37%) of the group with highest body mass index. Late systolic murmurs occurred alone or in combination with midsystolic clicks in 43% of subjects in group I, 26% of subjects in group II and 12% of group III (chi-square = 7.22, $p < 0.01$ vs group I). Typical auscultatory features of MVP were observed in more subjects with MVP in group I (71%) than in those in the other 2 groups (57% and 54%). Mitral clicks, murmurs or both were equally prevalent in men (63%) and women (60%).

These results indicate that MVP subjects with relatively low body weight have at least as high a prevalence of mitral systolic clicks and murmurs as those with body weight in the average normal to elevated range in relation to height. This finding is opposite to that predicted by the hypothesis that echocardiographic MVP associated with low body weight is a "variant of normal" unassociated with typical auscultatory features of MVP, and suggests that this hypothesis is incorrect. Our data support the view that lean subjects with inherited MVP also have blood pressure levels that are, on average, slightly lower than expected. Because only 4 subjects, at least 1 in each group, had holosystolic or nearly holosystolic murmurs of mitral regurgitation associated with left ventricular or left atrial dilatation, we are unable to determine whether the likelihood of developing hemodynamically important mitral regurgitation is related to body habitus in subjects with MVP. The older age and slight male predominance of the group with higher body mass index in the present study resembles the older age and male predominance we have previously found to characterize MVP patients with severe mitral regurgitation.[9] This suggests that this complication of MVP may be concentrated in MVP patients whose phenotype does not include a lean body habitus.

Further examination of our data reveals that the modest decrease in prevalence of auscultatory features among the MVP subjects with highest body mass index is due entirely to a strikingly lower prevalence of late systolic murmurs compared with lean subjects with MVP (12 vs 43%) that is not fully offset by a modest increase in the proportion of individuals who had isolated mitral systolic clicks (38 vs 26%). The greater chest wall thickness in less lean individuals with MVP might "damp" transmission to the chest

surface of soft systolic murmurs more than of higher intensity systolic clicks. The fact that almost all late systolic murmurs in our patients were of grade I or II/VI intensity is in accord with this possibility.

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Echocardiographic Evaluation of Obstructive Mechanism of Tetralogy of Fallot with Restrictive Ventricular Septal Defect

NORMAN N. MUSEWE, MB, ChB
JEFFREY F. SMALLHORN, MBBS
C.A.F. MOES, MD
ROBERT M. FREEDOM, MD
GEORGE A. TRUSLER, MD

Despite the trend toward earlier total surgical correction of tetralogy of Fallot, a number of complicating factors, most often related to unfavorable pulmonary arterial anatomy,[1] and, rarely, reduced left ventricular size,[2] may make palliation with a systemic to pulmonary arterial anastomosis necessary before corrective surgery. A restrictive ventricular septal defect (VSD) complicating tetralogy of Fallot is one of the less well-recognized features associated with a high mortality when surgical repair is delayed beyond infancy.[3-11] The echocardiographic recognition of this anomaly should be of importance because of the trend toward use of noninvasive diagnostic modalities in infants with various forms of congenital heart disease.[12] This study reviews echocardiographic features of tetralogy of Fallot in patients with a documented restrictive VSD, and examines the contribution of clinical findings to the diagnosis of this entity. The progression over time of VSD restriction and its impact on surgical management are also assessed.

From July 1983 to July 1987 a total of 80 new cases of tetralogy of Fallot were seen at the Hospital for Sick Children. Of these, 5 patients were identified as having a restrictive VSD during routine echocardiography. This time period was chosen because it coincided with the introduction of high resolution imaging and Doppler ultrasound at this institution. Four of the 5 patients had hemodynamic, angiographic and surgical confirmation of VSD restriction, with additional necropsy confirmation in 1. The fifth patient, who will be undergoing hemodynamic evaluation and surgery,

From the Departments of Pediatrics and Surgery, The University of Toronto Faculty of Medicine, and the Divisions of Cardiology and Cardiovascular Surgery, Departments of Pediatrics and Surgery, The Hospital for Sick Children, Toronto, Ontario, Canada. Manuscript received September 2, 1987; revised manuscript received and accepted November 9, 1987.

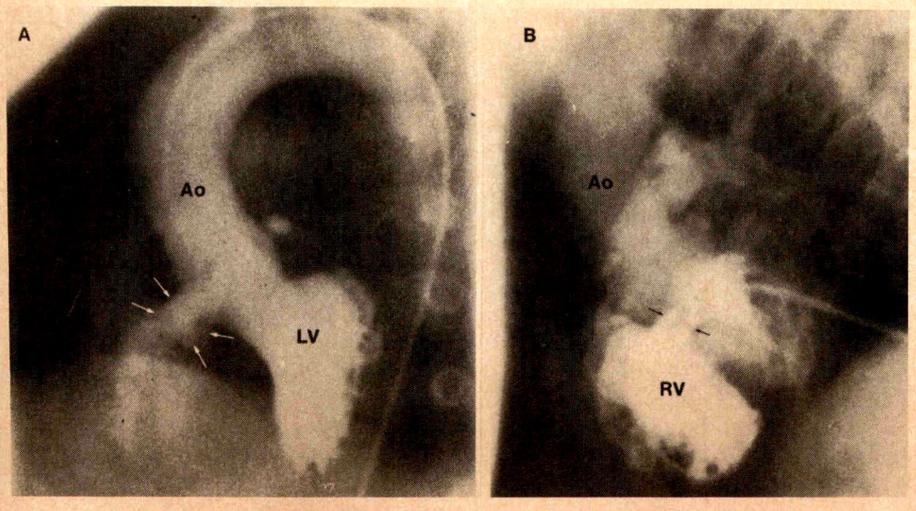

FIGURE 1. *A*, elongated left anterior oblique left ventricular angiocardiogram in patient no. 3 showing restrictive ventricular septal defect with jet of contrast. Accessory tricuspid tissue around the ventricular septal defect is demonstrated (*arrows*). *B*, left anterior oblique right ventricular angiocardiogram in the same patient showing restrictive jet across ventricular septal defect. Ao = ascending aorta; LV = left ventricle; RV = right ventricle.

TABLE I Hemodynamics at Cardiac Catheterization in Tetralogy of Fallot with Restrictive Ventricular Septal Defect (VSD)

	1	2	3	4	5
Age at catheterization	7 mos	22 mos	17 mos	3 days	—
RV systolic pressure (mm Hg)	185	130	122	100	—
LV systolic pressure (mm Hg)	120	92	91	70	—
VSD catheterization gradient (mm Hg)	60	38	31	30	—
Doppler echo VSD gradient (mm Hg)	*	35	36	31	49
Aortic oxygen saturation (%)	89	77	76	93†	—

Cardiac catheterization hemodynamics and angiographic findings compared with Doppler flow velocity across the VSD; hemodynamic and Doppler studies were not simultaneous.

Echo = echocardiographic; LV = left ventricular; RV = right ventricular.

* high velocity unresolved; † data obtained during infusion of prostaglandin E_1.

had VSD restriction defined by a high velocity Doppler jet from the right ventricle across the VSD. The remaining 75 cases had no evidence of VSD restriction as defined by echocardiographic, Doppler, hemodynamic or surgical evaluation.

The clinical features of each of the 5 patients were examined in an attempt to identify common features that might permit differentiation from those without VSD restriction. Where cardiac catheterization was carried out, hemodynamic measurements and angiocardiograms were examined and compared with echocardiographic findings. Anatomic features of VSD restriction obtained from surgical or necropsy records were also compared with the findings at echocardiography.

Serial echocardiograms were examined beginning with the earliest study that was available. These were performed using either the Hewlett Packard 77020 or ATL Utramark 8 ultrasound systems, both equipped with image-directed Doppler ultrasound. The VSD was evaluated from the subcostal and parasternal long- and short-axes, and the apical 5-chamber view. In addition to these views, the subxiphoid right oblique view[13] was used in 3 patients. Doppler flow velocities across the right ventricular outflow tract and the VSD were also evaluated. The degree of right ventricular hypertrophy, assessed by measurement of the dimension of the right ventricular free wall, was compared with measurements obtained in 5 age-matched patients of tetralogy of Fallot without evidence of VSD restriction. The ratio of right and left ventricular end-diastolic dimensions in the parasternal short-axis view in patients was also compared to that in the 5 control patients.

Mean age at diagnosis of the major cardiac lesion was 2 weeks. Cyanosis was recognized at a mean age of 7 weeks (range 1 to 28), and was graded as mild in 4 patients. One patient had cyanotic spells by 3 months of age. Electrocardiographic evidence of severe right ventricular hypertrophy with strain (inverted T waves and depressed ST segments) was present in 1 patient only (patient 4). None of the patients exhibited clinical signs of right-sided heart failure.

The data from the 4 patients who underwent cardiac catheterization are listed in Table I. Angiographically, the mode of VSD restriction was felt to be tricuspid septal leaflet or accessory tissue tags in each (Figure 1).

At surgery in 4 patients, accessory tricuspid valve tissue was noted inserting into the posterior and superior margins of the perimembranous malalignment ventricular septal defect, close to the aortic valve anu-

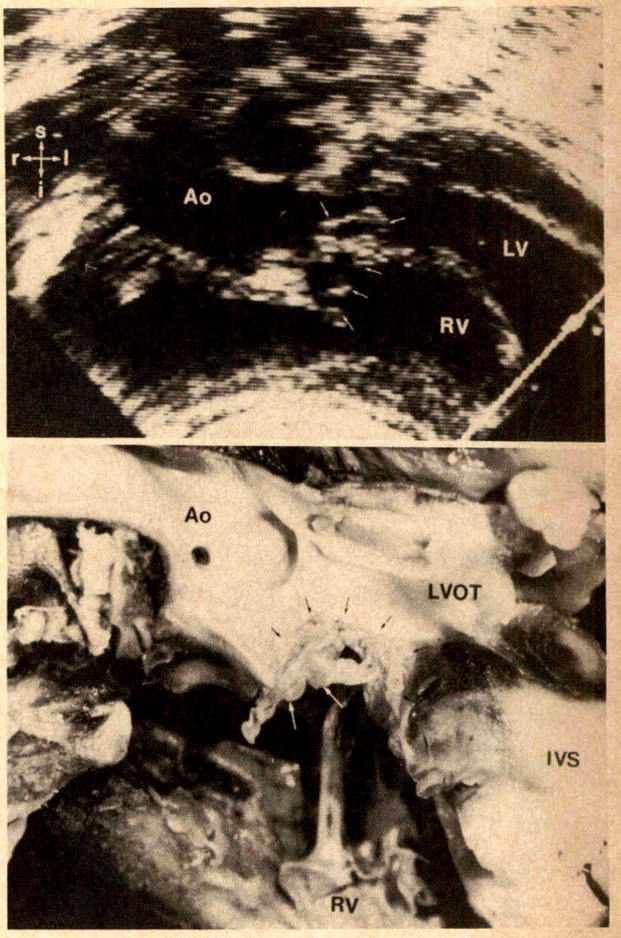

FIGURE 2. Two-dimensional echocardiographic-pathologic correlation of restrictive ventricular septal defect in patient 4. Subcostal long-axis view showing tricuspid tissue (*arrows*) protruding into left ventricular outflow tract (*top*). The same appearance is shown in the pathologic specimen (*bottom*). Ventricular septal defect margins are indicated by the *small arrows*. The ventricular septal defect patch is removed to facilitate visualization of accessory tricuspid tissue, which is seen attached to the superior margin of the ventricular septal defect (*large arrows*). Abbreviations as in Figure 1.

TABLE II Echocardiographic Measurements of Right Ventricular (RV) Free Wall Thickness and the Ratio of Right to Left Ventricular End-Diastolic Dimensions in Patients and Five Age-Matched Control Cases of Tetralogy of Fallot Without Ventricular Septal Defect Restriction

Pt No.	RV anterior wall thickness (mm)		RVED/LVED	
	P	C	P	C
1	10	4	.96	.61
2	7	5	.90	.65
3	6	4	.66	.56
4	5	3.5	1.16	.60
5	8	5	.72	.66

Measurements in patients and controls were performed from the parasternal short-axis view.

C = control; LVED = left ventricular end-diastolic dimension; P = patient; RVED = right ventricular end-diastolic dimension.

lus. Hypertrophied free wall and septal bands were also noted, but the latter did not contribute directly to the VSD obstruction in any of the patients.

Surgical repair involved detachment of the accessory tricuspid tissue from the margins of the defect followed by routine VSD closure in 3, while in the fourth patient, the accessory tissue was not resected, but was sutured to the VSD patch. This 3-day old patient died shortly after surgery. At autopsy, VSD restriction by tricuspid tissue was confirmed (Figure 2).

At least 2 serial 2-dimensional echocardiograms were available in 4 patients. The fifth patient (patient 4) had only 1 study. Data from patients and control cases are listed in Table II. Severe hypertrophy of both the right ventricular free wall and ventricular septum, with increased echodensity of the endocardial surface suggestive of endocardial fibrosis was seen in 1 patient (no. 1). The septal motion was flat in all patients.

In 4 patients, accessory tricuspid tissue was present within the VSD throughout the cardiac cycle. In these patients, the obstructing tissue was attached to the base of the infundibular septum, close to the aortic valve anulus. While this tissue moved anteriorly in diastole in the parasternal short-axis view, it bulged into the left ventricular outflow tract to variable degrees in systole. In 1 patient the accessory tissue protruded into subaortic area throughout the cardiac cycle. The echocardiographic and necropsy appearance in this patient are shown in Figure 2. In the fifth patient (no. 5, Figure 3), in contrast to the other 4, the obstructing tissue showed no attachments to the base of the infundibular septum. This tissue moved away from the VSD in diastole (Figure 3A), leaving it unobstructed, but moved into the VSD in early systole, occluding it until early diastole. (Figure 3B).

The mechanism of VSD obstruction in this patient appeared to involve suctioning of accessory tricuspid tissue into the defect at the onset of ventricular systole. This is further demonstrated in Figure 4, which uses the subxiphoid right oblique view in the same patient.

Obstruction of the VSD was recognized at the first 2-dimensional echocardiographic evaluation in 3 patients. On frame-by-frame review of the initial studies in each of the other 2 patients, the substrate for VSD restriction was already present. In 1 patient (no. 3), tissue could be intermittently seen within the VSD in both the parasternal long- and short-axis views. In this patient, the tissue appeared more obvious at the second study. The other patient (no. 5) had an accessory tricuspid tissue that was not attached to the base of the infundibular septum, but appeared in the VSD only during systole. This phenomenon was present but not recognized at the first study.

The results of Doppler evaluation of the VSD, performed in all patients at the last echocardiographic evaluation, are listed in Table I. Of the 4 patients who had more than 1 echocardiographic evaluation, 2 had serial Doppler performed across the VSD. In 1 (patient no. 1), a high velocity unresolved jet was present at 2 serial Doppler examinations. In the other (patient no. 2) low velocity left to right Doppler flow (2 m/s) was documented across the VSD at 2 earlier studies.

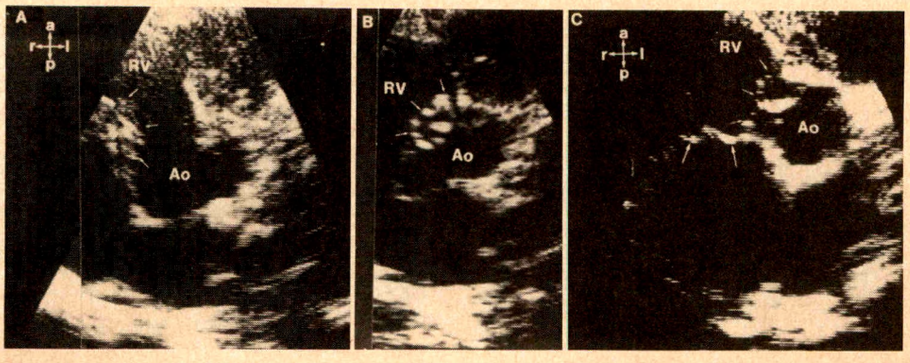

FIGURE 3. *A*, parasternal short-axis view in patient 5. The ventricular septal defect is wide open in diastole; accessory tricuspid tissue is indicated by *arrows*. *B*, the ventricular septal defect in the same patient is completely occluded by accessory tricuspid tissue in early systole. The obstructing tissue in this patient did not have attachments to the superior margin of the ventricular septal defect. *C*, in contrast to the patient shown in A and B, accessory tricuspid tissue was attached to the base of the infundibular septum in this patient (*small arrows*), resulting in its appearance within the defect throughout the cardiac cycle. A systolic frame is shown. The *large arrows* indicate the septal and superior leaflets of the tricuspid valve in a closed position. Abbreviations as in Figure 1.

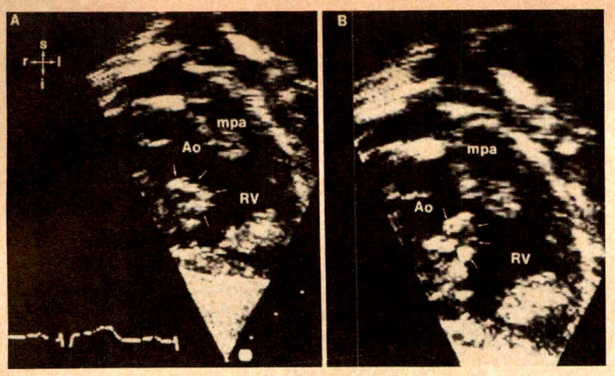

FIGURE 4. *A*, subxiphoid right oblique views in the same patient as in Figure 3 (A and B). In diastole the accessory tricuspid tissue moves away from the ventricular septal defect, leaving it unobstructed (*arrows*). *B*, in ventricular systole, this tissue moves into the ventricular septal defect, almost completely occluding it. Both outlets, the infundibular septum and the ventricular septal defect are well profiled in this view. mpa = main pulmonary artery; other abbreviations as in Figure 1.

At the last study, however, the Doppler flow was right to left.

The first description of a restrictive VSD in tetralogy of Fallot is attributed to Soulié et al[3] in 3 of 22 patients with tetralogy of Fallot and suprasystemic right ventricular pressures. Various other investigators[4–11,14] have subsequently described this uncommon entity.

While earlier reports[4,5] emphasized the clinical signs that might lead to suspicion of this complication in tetralogy of Fallot, they relied almost entirely on the use of phonocardiography for the detection of subtle changes in quality and duration of the systolic ejection murmur to differentiate this entity from classic tetralogy of Fallot. Although Neufeld et al[5] described 3 older patients with forceful right ventricular impulses and distended jugular veins, features not normally seen in tetralogy of Fallot, in most patients clinical features were not helpful in making the diagnosis of a restrictive VSD before cardiac catheterization.

Clinical suspicion of a restrictive VSD may therefore depend on detection of an unusually increased right ventricular precordial impulse or increased jugular venous pressure, signs that may be difficult to elicit in small infants. The finding of severe right ventricular hypertrophy and strain on electrocardiography may be helpful in patients with early severe obstruction to the VSD. In this study, however, we could not identify any consistent clinical features suggestive of VSD restriction.

In most of the reported cases of tetralogy of Fallot or pulmonary atresia,[9] VSD restriction has been due to tricuspid septal leaflet or accessory tissue anomalously inserting into the margins of the defect. VSD restriction due to a truly small defect must be very rare. In the most detailed morphologic description of VSD restriction in tetralogy of Fallot[10] it was divided into "mobile" and "fixed" types, depending on the mobility of the accessory tricuspid tissue. In this study[10] the authors suggested that, because of the possibility of subaortic obstruction, the mobile tissue should be completely excised, or the VSD patch placed such that the accessory tissue is left on the right ventricular aspect of the septum.

In all the patients in this study, restriction was similarly due to accessory tricuspid tissue, and could be potentially recognized by echocardiography as early as the newborn period. It therefore appears that the substrate for VSD restriction, when it occurs, is present as an integral part of the pathology of tetralogy of Fallot.

Careful evaluation of the VSD is essential as the absence of tissue occluding the defect throughout the cardiac cycle does not preclude restriction, as was seen in 1 of our patients. We speculate that in this case, unlike the other 4, a "venturi" type effect played a significant role in suctioning the accessory tissue into the VSD during systole, thereby obstructing it.

When obstructing tissue is not attached to the infundibular septum, specific diagnosis rests on slow frame-by-frame examination of the excursion of accessory tricuspid tissue, because obstruction of the VSD occurring in systole only may be missed during real-time examination, especially at rapid heart rates. Although significant left ventricular outflow obstruction by accessory tricuspid tissue was not present in any of our patients, the surgeon should probably excise this tissue where possible, regardless of its mobility, except where excision might affect the integrity of the tricuspid valve.

Doppler echocardiography plays an important role in identifying VSD restriction. Caution must be taken not to dismiss a potentially restrictive VSD as nonobstructive if the substrate exists in the absence of a documented gradient. In this setting, decompression through a relatively unobstructed right ventricular outflow tract may be responsible for the lack of a pressure difference between the 2 ventricles. It is also possible that the VSD tissue may proliferate in a manner similar to that encountered in perimembranous ventricular septal defects,[15] leading to progressive restriction.

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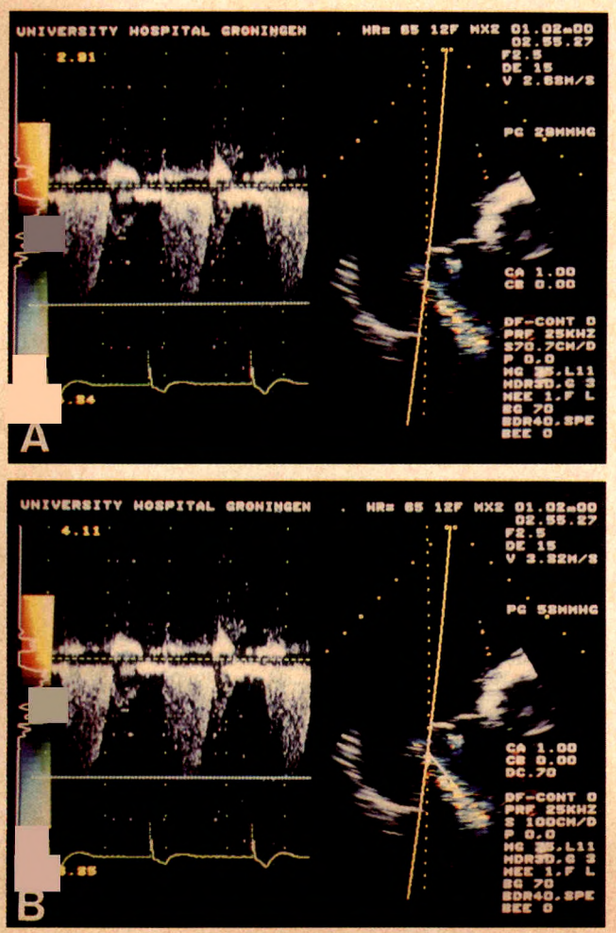
Noninvasive Measurement of Right Ventricular Systolic Pressure by Combined Color-Coded and Continuous-Wave Doppler Ultrasound

HANS P.M. HAMER, MD, PhD
BERT L. TAKENS, MD
JAN L. POSMA, MD
KONG I. LIE, MD, PhD

Noninvasive prediction of right ventricular (RV) pressure is a clinical challenge.[1-4] Doppler echocardiography is now routinely used to assess pulmonary hypertension.[5-10] Measurement of the flow velocity of tricuspid regurgitation is of great value in the evaluation of RV peak pressure. Without a pressure difference across the pulmonary valve, peak pressure in the pulmonary artery can be calculated from the flow velocity of the tricuspid regurgitation. Correlations with catheterization data are reasonably good, although in most studies extreme values are included in the calculations and this may result in unrealistically good correlations with catheterization data. Without visualization of the direction of the tricuspid regurgitation, underestimation of RV peak pressure can be expected in a number of patients because the direction of the tricuspid regurgitation flow is not necessarily the same as the Doppler sound beam. One still needs to search and listen for audio Doppler signals to record the measured maximal velocity. We undertook this study, therefore, attempting to answer the following questions: (1) Can continuous-wave (CW) Doppler alone accurately pre-



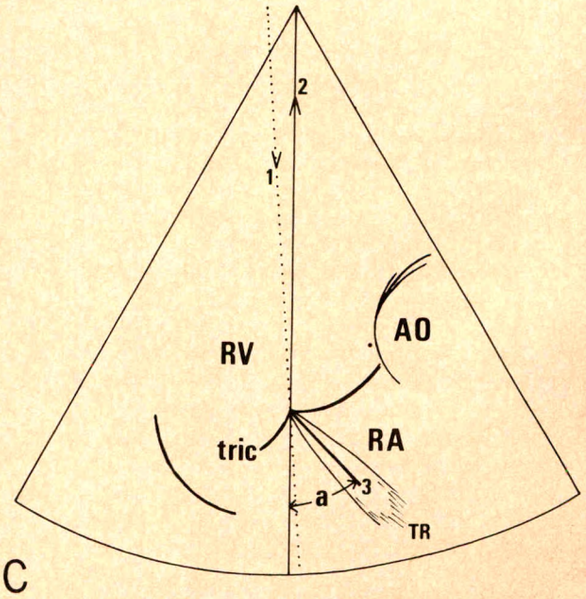


FIGURE 1. CC and CW Doppler echocardiograms without angle correction (*A*, peak pressure 29 mm Hg) and with angle correction (*B*, peak pressure 58 mm Hg), showing the method of establishing the angle between directions of CW sound beam and CC Doppler flow jet (*C*). a = angle; AO = aorta; RA = right atrium; RV = right ventricle; TR = visualized tricuspid regurgitation; tric = tricuspid valve; 1 = CW Doppler sound beam; 2 = direction of the receiving CW signal; 3 = line with which the angle is established.

From the Department of Cardiology, University Hospital Groningen, Groningen, The Netherlands. Manuscript received July 13, 1987; revised manuscript received October 10, 1987, and accepted October 25.

dict the RV peak pressure and what would be the correlation between Doppler and catheterization data in that most interesting group of patients, those with moderately elevated RV peak pressures? (2) Is the angle between the visualized tricuspid regurgitation with color-coded (CC) Doppler and the CW beam of importance for accurate measurement of the RV peak pressure? (3) In what percentage of patients can pulmonary hypertension be suspected by auscultation or phonocardiography?

CW and CC Doppler ultrasound examinations were performed in 51 patients undergoing right-sided heart catheterization. The group consisted of patients who consecutively underwent diagnostic catheterization for left-sided heart disease or for electrophysiologic investigations. The patients were clinically stable and had no change in therapy during several days before measurements. Doppler examinations were done 3 hours before catheterization. The group consisted of 31 men and 20 women, ages 19 to 73 years (54 ± 15). Sinus rhythm was present in 48 patients, 2 had a pacemaker rhythm and 1 had atrial fibrillation. On the basis of RV pressures at catheterization, patients were divided into 2 groups. Group 1 consisted of 16 patients with RV pressures <35 mm Hg and group 2 consisted of 35 patients with RV pressures ≥35 mm Hg.

Auscultation was performed with the patients supine, paying special attention to the loudness of the pulmonic closure sound and to the presence of a tricuspid regurgitation murmur. Phonocardiograms were made at the fourth rib at the left and right side of the sternum with cutoff frequencies of 35, 70, 140 and 240 Hz, together with a carotid pulse recording for definition of the pulmonic closure sound.

Doppler examinations were performed with a commercially available phased array echocardiograph with CC and CW Doppler (Toshiba 65A). A 2.5-MHz transducer was used for all studies. The patients lay in left lateral position. To find the best position for visualization of the tricuspid regurgitation, the parasternal, apical and subxyphoidal positions were investigated. The CC Doppler flow jet had to originate from the valve itself. This point was positioned in the middle of the sector image (Figure 1). The transducer was then turned around its long axis to obtain the largest angle and exclude the error created when the color flow jet has an angle in respect to the sector plane. The CW Doppler sound beam was arranged through the point of the tricuspid valve where the leakage was seen. The receiving Doppler signal line was positioned through the same point. From the best CW signal, also obtained by listening for the audio signals, maximal velocity was measured and pressure difference across the tricuspid valve calculated by means of the simplified Bernoulli equation $p = 4v^2$. The angle between CW and CC flow jet directions was established by positioning a line through the CC flow jet. This line originated form the crosspoint of both CW lines. The machine calculated the angle and corrected the CW measurement for it by using v-corrected = v-uncorrected/cos α. The peak transtricuspid pressure difference was judged to be the same as the RV peak pressure: in case of a slight tricuspid regurgitation the early

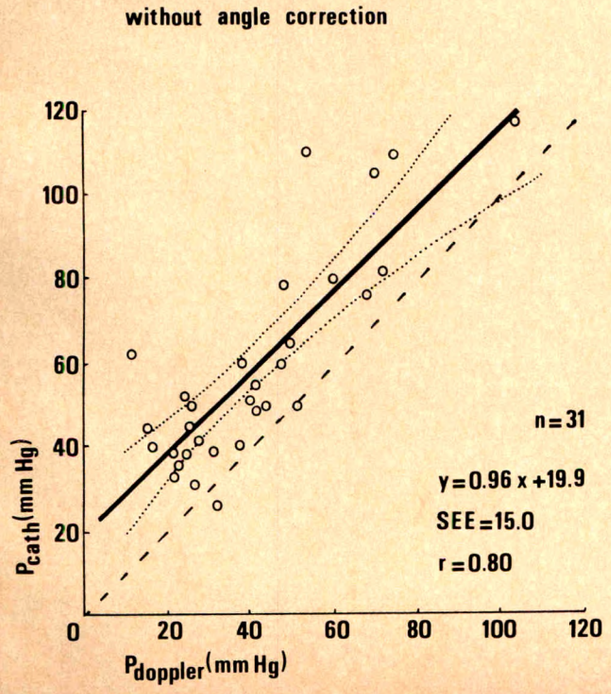


FIGURE 2. Correlation between measurements of RV peak pressures with CW Doppler and with catheterization for the 31 patients with visible and measurable tricuspid regurgitation without angle correction. The correlation is r = 0.80 (p <0.001).

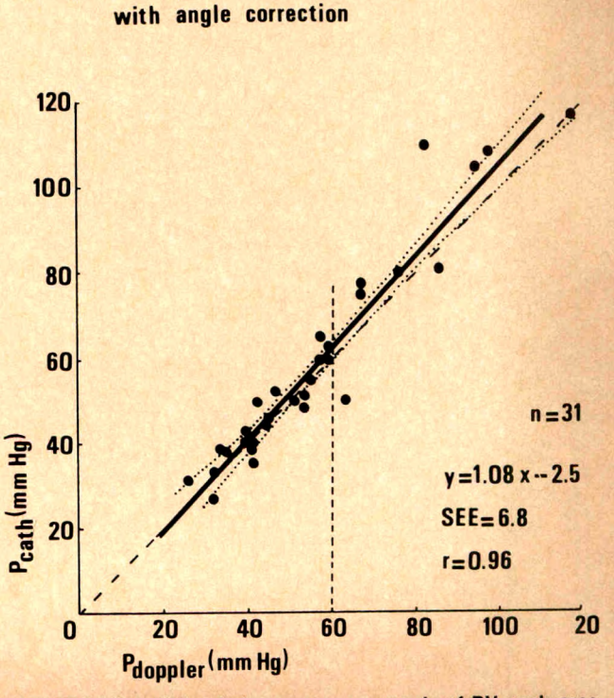


FIGURE 3. Correlation between measurements of RV peak pressures with CW Doppler and with catheterization for the 31 patients with visible and measurable tricuspid regurgitation with angle correction. The correlation is r = 0.96 (p <0.001).

systolic right atrial pressure is much lower than the mean right atrial pressure.

Doppler measurements were made by 2 investigators in separate sessions without knowledge of their results and of the results of catheterization measurements. Ten beats were analyzed in case of a sinus rhythm and at least 25 beats in case of atrial fibrillation. Measurements were made during end-expiratory periods. During catheterization, pressures in RV and pulmonary artery were measured at end-expiration. The patients did not have premedication.

The data are expressed as mean ± standard deviation. Linear regression analysis was used to assess the correlation between Doppler and catheterization RV pressures. Comparisons among groups were made with the unpaired Student t test and chi-square for nonpaired data and the McNemar test for paired data.

A pressure difference between RV and pulmonary artery was not found in any of the patients. For the 16 patients in group 1 the mean peak RV pressure was 27 ± 5 mm Hg (range 16 to 33); for the 35 patients in group 2 it was 58 ± 23 mm Hg (range 36 to 118).

Tricuspid regurgitation could be visualized with CC and also be measured with CW in 3 patients (19%) in group 1 and in 28 patients (80%) in group 2 ($p < 0.001$). For 17 patients in group 2 the transducer position was in the short axis of the aorta, for 9 patients it was at the apex and for 2 the location was subxyphoidal. An angle of <20° was found in 3 patients, 20 to 39° in 17 and ≥40° in 8.

For the 3 patients in group 1 and the 28 in group 2, the correlations between Doppler and catheterization measurements, with and without angle correction, are presented in Figures 2 and 3. By excluding extreme values (angle-corrected values >60 mm Hg), 22 of the 31 patients continued participating. All the excluded patients had RV pressures ≥50 mm Hg at catheterization. Without angle correction, a poor correlation was found for this important group of patients with moderately elevated RV peak pressures. However, the correlation was good with angle correction (Figures 4 and 5).

Without angle correction (CW alone), elevated RV pressures were detected in only 16 out of 28 patients in group 2 (sensitivity = 46%). With angle correction, 27 of the 28 patients were detected (sensitivity = 77%), a significant improvement over the results without angle correction ($p < 0.005$).

For smaller angles (<30°) the correlation was r = 0.94 after correcting for pressure differences (which remained good for larger angles, with r = 0.93).

At auscultation, 4 patients (11%) had a tricuspid regurgitation murmur. Patients with mitral regurgitation were excluded. A loud pulmonic closure sound (louder than the aortic closure sound at the fourth rib) was heard in 9 patients (26%). At phonocardiography, 12 patients (34%) had evidence of pulmonary hypertension according to the loudness of the pulmonic closure sound. There was no correlation between the magnitude of the pulmonary artery pressure and the splitting of the second heart sound.

The advantage of CC Doppler is that the angle between the CW Doppler sound beam and the direction of the tricuspid regurgitation can be visualized and the measurements corrected for this angle. The results of this study indicate that angle correction is important for calculating RV peak pressures and thus, in the

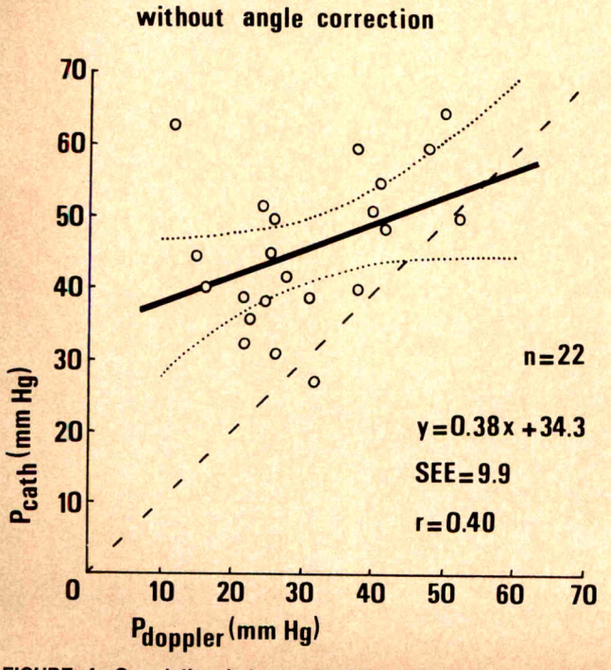


FIGURE 4. Correlation between angle-uncorrected Doppler RV peak pressures and catheterization measurements for the 22 patients with Doppler pressures ≤60 mm Hg. The correlation is r = 0.40 (not significant).

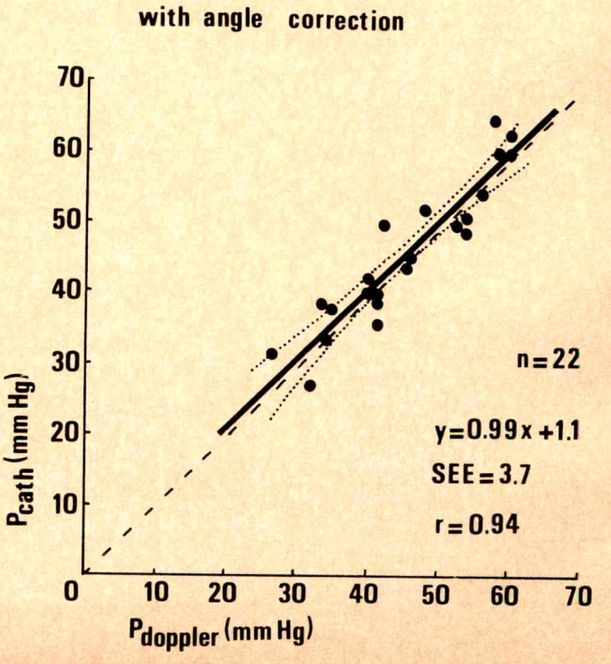


FIGURE 5. Correlation between angle-corrected Doppler RV peak pressures and catheterization measurements for the 22 patients with Doppler pressures ≤60 mm Hg. The correlation is r = 0.94 ($p < 0.001$).

absence of a pressure difference across the pulmonic valve, for pressures in the pulmonary artery.

The angles we found were rather large, but good correlations were found for even larger angles. Measurements were highly reproducible: interobserver variability was low and with a discrepancy of 1.8 ± 2.2 mm Hg.

In elevated RV peak pressures, tricuspid regurgitation could be found in 32 of 35 patients with CC or CW, or both. In 7 patients there was only a CC signal, or only a CW signal, or the angle could not be established. In such patients, pulsed Doppler measurements in the pulmonary artery can be helpful in determining the pressure in the pulmonary artery. Both angle visualization and CW measurement were possible in 28 of 35 patients (80%), which is about the same percentage found in the literature for CW measurements alone. Without angle correction only 57% of the patiens (16 of 28) were recognized with elevated pressures, whereas with angle correction this figure was 96% (27 of 28), which makes angle correction clinically important.

Combined CC and CW Doppler echocardiography provides a rather simple, very accurate and highly reproducible method for calculation of the peak RV pressure and thus—in the absence of pulmonic stenosis—the peak pressure in the pulmonary artery. The method gives excellent results and is a very important tool for use in patients with mild pulmonary hypertension. For this particular group of patients, the addition of color Doppler has proven to be valuable.

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The AJC in March 1963

WILLIAM C. ROBERTS, MD

The AJC in March 1963 contained 21 articles occupying 140 pages, including 1 editorial, 11 major studies, 3 experimental (nonhuman) studies and 6 case reports. This piece will comment on 5 articles.

In a superb editorial entitled "Diet and atherosclerosis: truth and fiction" Snapper[1] from Brooklyn, New York, logically showed the detrimental influence of cholesterol intake and the lowering effect of polyunsaturated fatty acids on the serum total cholesterol level. He pointed out areas of the world where atherosclerosis is rare and cholelithiasis and phlebothrombosis "hardly ever occur." He stated that ". . . a diet devoid of cholesterol but rich in polyunsaturated acid prevents the *deposition* of cholesterol within the intima of arteries . . . . A diet with a high proportion of polyunsaturated fatty acids, begun in early childhood as a life-long regimen, will *prevent* the development of atherosclerosis, thrombosis and cholelithiasis."

Shubin and Weil[2] from Los Angeles, California, measured serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and lactic dehydrogenase (LD) in 43 patients with shock caused by noncardiac conditions (hemorrhage, infection, neurologic injury and vascular obstruction). They found these levels to be elevated in 70%, 37% and 52%, respectively, indicating that elevations of these enzymes are not helpful in differentiating shock secondary to acute myocardial infarction from that caused by noncardiac conditions. Klein and Palmer[3] from San Diego, California, found a much higher elevation of SGOT and LD in patients with acute myocardial infarction associated with shock than in patients with uncomplicated acute myocardial infarction.

Greenwood and associates[4] from Toronto, Canada, analyzed results of closed mitral commissuratomy in 88 patients operated on by W.G. Bigelow between March 1951 and June 1953 and compared his results with those of 172 patients with mitral stenosis without operation but with a similar follow-up period. They concluded that mitral commissurotomy prolonged life, improved funtional capacity, prevented recurrence of hemoptysis (as long as the obstruction remained relieved) and reduced both the occurrence and recurrence of systemic embolism. If calcific deposits had been present in the stenotic valve, however, the 5-year results of commissurotomy were poor, with only 1 in 4 patients being improved over 5 years.

Samet and associates[5] from Miami Beach, Florida, using a "cardiac catheter electrode pacemaker" inserted in an antecubital vein and passed to the right ventricular outflow tract, treated 4 patients with complete heart block complicating acute myocardial infarction. Dramatic clinical improvement resulted from catheter-electrode pacemaking in all 4 patients.

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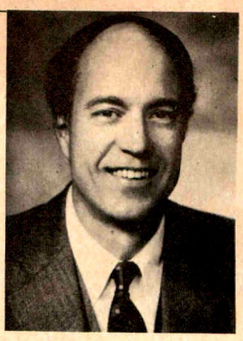


The AJC in 1987

The year 1987 was a good one for the AJC. A total of 2,833 pages for articles (2,810 pages) and letters (23 pages) was published in the 16 regular issues of the AJC in 1987 (Table I). This number represents an increase of 189 pages (7%) for articles and letters compared to 1986. In addition to these 2,833 pages, 395 other editorial (i.e., nonadvertising) pages were published in the regular issues in 1987. Of this number, 202 were used for the "contents with abstracts," and I am pleased to report that the publisher is considering discontinuing this section in July 1988. The publisher also will change the layout of the "contents in brief" in July 1988.

The number of articles published in the regular issues in 1987 was 695, an average of 58 each month, and an increase of 79 articles (11%) compared to 1986 (Table I). Each of the 695 articles averaged 4.04 pages in length, a 5% decrease in average article length compared to the preceding year. Although the percent of articles in each of the various categories in 1987 was roughly similar to what it had been in 1986, the number of articles on systemic hypertension increased to 28 from 10 in the preceding year (Table I). Because systemic hypertension is such a common condition (60 million Americans have it), articles on this subject should, in my view, occupy more than 4% of the articles published. No experimental articles were published in 1987 (except those which could fit into the Brief Report format).

I am enormously pleased about how the *Brief Reports* section of the AJC has developed during the past 5.5 years. This section was initiated in September 1982. In 1983, 65 (80%) of the 81 brief reports published were single-case studies (Table II); in 1984, 122 (60%) of the 204 brief reports published were single-case studies; in 1985, 54% were single-case studies and in 1987 only 34% of the 203 brief reports published were single-case studies. In 1987, 33% of the brief reports involved >10 patients and many involved >100 patients. It is clear that the Brief Reports section of the *Journal* is no longer a case-report section. To emphasize this change, beginning in April 1988 the reports which include case descriptions will be placed in a new section to be called simply *Case Reports*. The Brief

TABLE I Number of Pages and Types of Articles Published in the Regular Issues of the AJC in 1983 to 1986

	1983	1984	1985	1986	1987
Number of pages (mean/month)	3,435 (286)	3,403 (284)	3,014 (251)	3,004	3,228
For articles (pages/article)	3,130 (4.87)	3,077 (4.12)	2,623 (4.07)	2,627 (4.26)	2,810 (4.04)
For letters (number) [no. with replies]	27 (53) [40]	36 (80) [38]	21 (40) [16]	17 (40) [8]	23 (45) [18]
For staff, editorial board	15	15	17	16	16
For contents in brief	28	31	44	44	50
For contents with abstracts	142	145	207	179	202
For volume indexes	79	69	70	86	101
For information for authors	12	15	17	15	16
For other	2	15	15	20	10
Number of articles (mean/month)	643 (54)	747 (62)	645 (54)	616 (51)	695 (58)
Coronary artery disease	132 (21%)	140 (19%)	138 (21%)	153 (25%)	180 (27%)
Arrhythmias and conduction defects	74 (12%)	76 (10%)	71 (11%)	86 (14%)	83 (12%)
Systemic hypertension	18 (3%)	19 (3%)	15 (2%)	10 (2%)	28 (4%)
Congestive heart failure	22 (3%)	16 (2%)	18 (3%)	21 (3%)	25 (3%)
Valvular heart disease	47 (7%)	37 (5%)	29 (5%)	39 (6%)	30 (4%)
Cardiomyopathy	22 (3%)	18 (2%)	9 (1%)	7 (1%)	14 (2%)
Congenital heart disease	79 (12%)	47 (6%)	38 (6%)	34 (6%)	31 (4%)
Miscellaneous	44 (7%)	41 (5%)	41 (7%)	44 (7%)	26 (4%)
Methods	29 (5%)	31 (4%)	21 (3%)	9 (1%)	24 (3%)
Experimental studies	52 (8%)	64 (9%)	49 (8%)	4 (1%)	0
Editorials	19 (3%)	28 (4%)	16 (3%)	21 (3%)	26 (4%)
Brief reports	81 (13%)	204 (27%)	172 (27%)	160 (26%)	203 (29%)
Historical studies	2 (<1%)	0	3 (1%)	5 (1%)	7 (1%)
AJC 25 years ago	8 (1%)	11 (2%)	13 (2%)	11 (2%)	6 (1%)
From-the-editor columns	14 (2%)	15 (2%)	12 (2%)	12 (2%)	12 (2%)

TABLE II Brief Reports in the AJC 1983 to 1987

	1983	1984	1985	1986	1987
No. of reports (no./month) (% of total)	81 (7) (13%)	204 (17) (27%)	172 (14) (27%)	160 (13) (26%)	203 (17) (29%)
No. of pages (no./month) (% of total)	123 (10) (4%)	308 (26) (10%)	278 (23) (11%)	276 (23) (11%)	367 (31) (13%)
No. of patients in each report					
0	1 (1%)	0	7 (4%)	1 (<1%)	7 (3%)
1	65 (80%)	122 (60%)	93 (54%)	83 (52%)	68 (34%)
2	9 (11%)	33 (16%)	18 (10%)	11 (7%)	18 (9%)
3	5 (6%)	12 (6%)	5 (3%)	8 (5%)	10 (5%)
4	0	8 (4%)	3 (2%)	8 (5%)	9 (4%)
5	0	5 (2%)	6 (3%)	6 (4%)	3 (2%)
6–10	1 (1%)	4 (2%)	12 (7%)	16 (10%)	21 (10%)
11–25	0	9 (4%)	13 (8%)	12 (7%)	23 (11%)
26–50	0	3 (1.5%)	6 (4%)	4 (2%)	15 (8%)
>50	0	7 (3%)	9 (5%)	11 (7%)	29 (14%)
No. of figures (no./report)	183 (1.49)	432 (1.40)	302 (1.76)	254 (1.59)	336 (1.66)
No. of tables (no./report)	22 (0.18)	56 (0.27)	57 (0.33)	76 (0.48)	142 (0.70)

TABLE III Subjects of Brief Reports in the AJC 1983 to 1987

	1983	1984	1985	1986	1987
Coronary artery disease	19 (23%)	33 (16%)	39 (23%)	25 (16%)	57 (28%)
Arrhythmias and conduction defects	15 (19%)	45 (22%)	26 (15%)	39 (24%)	34 (17%)
Systemic hypertension	0	1 (<1%)	0	2 (1%)	2 (1%)
Congestive heart failure	0	2 (1%)	2 (1%)	3 (2%)	4 (2%)
Valvular heart disease	7 (9%)	16 (8%)	17 (10%)	22 (14%)	33 (16%)
Cardiomyopathy	7 (9%)	14 (7%)	11 (6%)	7 (4%)	8 (4%)
Miscellaneous topics	19 (23%)	46 (23%)	37 (22%)	29 (18%)	28 (14%)
Congenital heart disease	13 (16%)	43 (21%)	34 (20%)	27 (17%)	29 (14%)
Methods	0	4 (2%)	4 (2%)	0	2 (1%)
Experimental studies	1 (1%)	0	2 (1%)	3 (2%)	6 (3%)
Historical studies	0	0	0	3 (2%)	0
Totals	81	204	172	160	203

TABLE IV Symposia Published in the *American Journal of Cardiology* in 1987

Number	Month, Day	Title	Guest Editor(s)	Articles	Pages	Sponsor	Date of Symposium	Interval (months) Symposium to Publication
A	January 23	Calcium Ion, Cardiac Myocyte, Vascular Smooth Muscle in Hypertension	Edward D. Frohlich	19	121	Marion Laboratories	March 27–29, 1986	10
B	January 30	Calcium Antagonists	Eugene Braunwald	25	187	Sandoz Pharmaceuticals	Sept. 11–12, 1986	4
C	March 9	Total Ischemic Burden	Attilio Maseri	7	38	Pfizer Laboratories	September 14, 1986	5
D	April 24	Ramipril—A New Angiotensin Converting Enzyme Inhibitor	J. Ian S. Robertson	31	177	Hoechst AG	May 2–4, 1986	11
E	April 30	Proarrhythmia	Leonard N. Horowitz Douglas P. Zipes	10	56	Berlex Laboratories	March 9, 1986	14
F	May 15	Betablockade, Cardioselectivity and Intrinsic Sympathomimetic Activity	Aram V. Chobanian Stanley H. Taylor	12	54	Wyeth Laboratories	Sept. 28–29, 1986	8
G	May 29	Doxazosin	Klaus Starke	18	104	Pfizer International	June 7, 1986	11
H	June 15	Pirmenol	H. Just	12	57	Warner-Lambert	December 2, 1985	19
J	June 30	Nicardipine	William W. Parmley	8	37	Syntex International	September 13, 1986	9
A	July 15	Cardioprotection in Ischemic Heart Disease	Desmond Julian	8	41	ICI Pharmaceuticals	January 18, 1986	18
B	July 31	Restenosis After PTCA	Spencer B. King, III	16	69	USCI, Division of C.R. Bard	June 7, 1986	14
C	August 14	Enoximone for Heart Failure	Karl T. Weber	18	90	Merrell Dow Research Institute	September 14, 1986	11

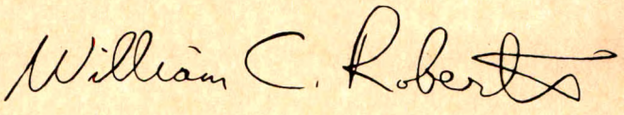
TABLE IV Symposia Published in the *American Journal of Cardiology* in 1987 (*cont'd.*)

Number	Month, Day	Title	Guest Editor(s)	Articles	Pages	Sponsor	Date of Symposium	Interval (months) Symposium to Publication
D	August 31	Beta blockers as Anti-Arrhythmic Agents	Joel Morganroth	12	67	Princeton Pharmaceutical Products (Squibb)	December 12–13, 1986	8
E	September 18	Beta Blocker with ISA for Hypertension	William C. Roberts	7	37	Rhône-Poulenc Santé	June 23–27, 1986	15
F	October 16	Moricizine HCl	Bernard Lown	14	89	Du Pont	April 20, 1985	28
G	October 30	New Approaches to Cardiovascular Therapy	George L. Blackburn	15	93	Sandoz Pharmaceuticals	March 5–8, 1987	8
H	November 16	Nitroglycerin	Jonathan Abrams	10	48	W. H. Rorer	September 13, 1986	14
I	December 14	Hypertension—The Heart and Kidney	Edward D. Frolich	24	132	Marion Laboratories	April 9–11, 1987	8
J	December 28	Behavioral Disorders in Heart Disease	Sheldon H. Gottlieb Rudolf Hoehn-Saric	13	79	Upjohn	April 3–4, 1987	9

Reports will be reserved for major studies that are concise and have only 1 or 2 major points. At least a third of the articles published as Brief Reports were initially submitted as regular length articles but converted to the shorter format. I urge the readership to examine the brief reports more carefully because these reports provide the most information per page of any section in the *Journal*. The topics of the Brief Reports in 1987 were roughly similar to what they had been in 1986 (Table III). The editor particularly welcomes reader reaction to the Brief Reports.

And 1987 also was a good year for supplements. A total of 19 supplements was published in the AJC, and they included 279 articles occupying 1,576 pages (Table IV). Some of the more prominent cardiovascular investigators in the world served as guest editors of these supplements. The average interval between the symposium meeting and the publication of the proceedings of the symposium was 12 months. Supplements are published, however, within 3 months of receipt of all the manuscripts by the editor.

Thus, including both regular issues and supplements a total of 974 articles occupying 4,412 pages was published in the AJC in 1987. At a yearly subscription cost of $66.00, each article in 1987 cost a subscriber <7 pennies and each page for articles and letters, <2 pennies. The subscription cost throughout 1988 will remain the same as in 1987, so the *Journal* in 1988 should be an even better bargain.



William C. Roberts, MD
Editor-in-Chief

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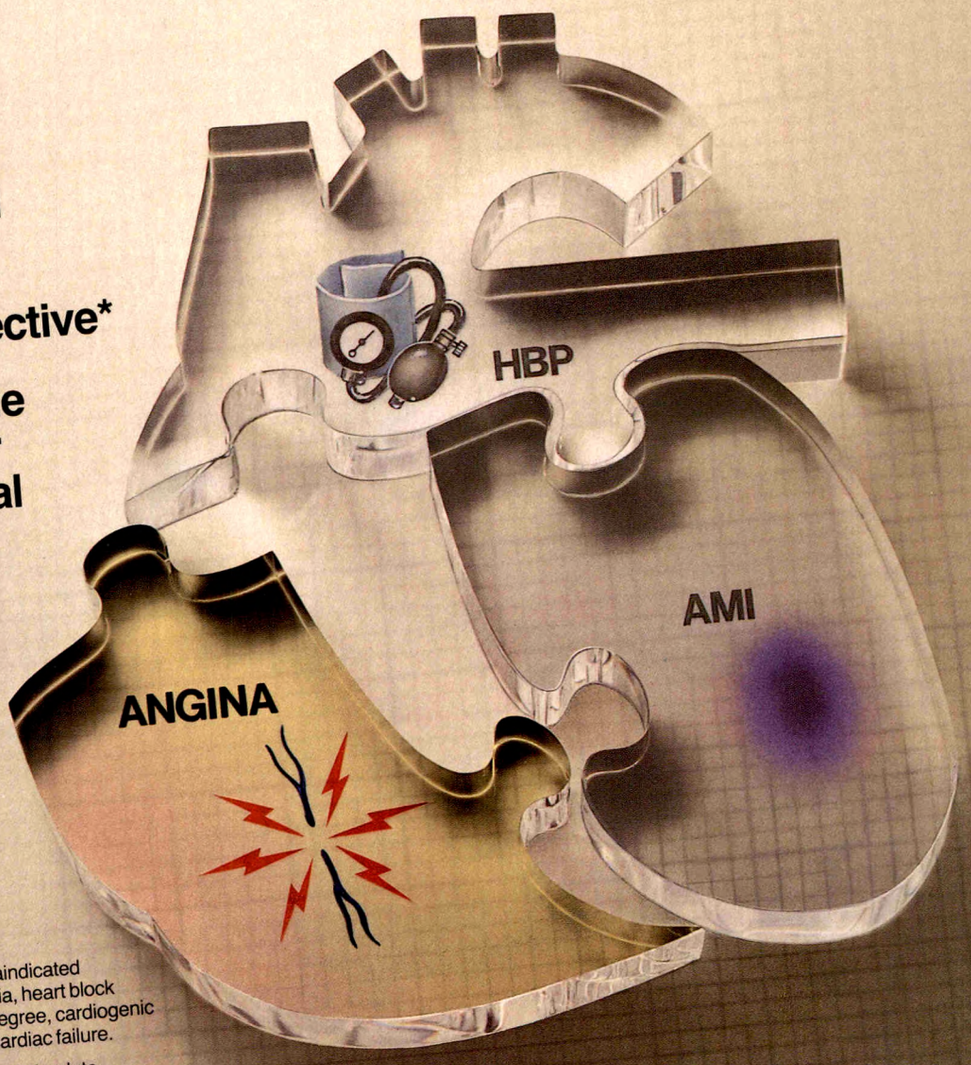

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Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.
Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.
Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.
Treatment
There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

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LETTERS

SPASM OF SAPHENOUS VEINS USED AS CONDUITS FOR AORTOCORONARY BYPASS GRAFTING

I read the brief report by Mann and associates on morphologic documentation of spasm of a saphenous vein used as a coronary conduit.[1] The statement was made that spasm of a saphenous vein used as an aortocoronary conduit had not been reported. In actuality, at least 4 reports of documented spasm in an aortocoronary saphenous vein graft have appeared.[2-5] Yours was a most interesting case in that it had autopsy demonstration of persistent spasm.

GERALD M. LAWRIE, MD
Houston, Texas
30 April 1987

In the article by Mann et al[1] regarding aortocoronary vein graft spasm, the assertion is made that "Spasm of saphenous veins used as aortocoronary conduits has not been reported." This is incorrect. It is, however, the first case in which the diagnosis has been at autopsy. The first report of spasm occurring in an aortocoronary vein graft was by Victor et al.[2] A commentary by Heupler[6] accompanied the article. In that commentary, Heupler reported another case of vein graft spasm that had been observed during surgery at the Cleveland Clinic. I presented 2 such cases at the meeting of the Section on Cardiovascular Surgery at the 49th Annual Scientific Assembly of the American College of Chest Physicians in October 1983. My second case was serendipitously recorded on video tape in the operating room. The video tape clearly showed the area of spasm and its dramatic response to treatment. The case described by Victor et al documented angiographically the existence of the spasm and its successful treatment. In each one of these cases (except for that described by Mann et al) the patients survived as a result of prompt recognition of the problem and treatment by direct intracoronary nitroglycerin infusion either in the catheterization laboratory or in the operating room.

As I stated in my presentation at the American College of Chest Physicians and as Heupler pointed out in his commentary, vein graft spasm should be considered in any patient with aortocoronary vein grafts who experiences sudden deterioration in hemodynamics associated with signs of acute ischemia. Confirmation of diagnosis and treatment can be accomplished either by direct observation in the operating room or by angiographic evaluation, and treatment with intracoronary nitroglycerin infusion should be started immediately.

THOMAS J. BERGER, MD
Great Falls, Montana
5 May 1987

REPLY: We thank Drs. Lawrie and Berger for their good letters. They are right. We examined the 5 articles[2-6] brought to our attention and certain data in the 6 patients described in them are summarized in Table I. Coronary angiography was prompted after coronary artery bypass grafting (CABG) in 4 of the 6 patients because of recurrence of angina pectoris. In these 4 patients, the interval from CABG to postoperative coronary angiography ranged from 60 to 180 days (mean 139). The other 2 patients had no recurrence of symptoms after CABG, but had coronary angiography, nevertheless, 7 and 990 days after CABG. In 5 patients, spasm of a saphenous vein used as an aortocoronary bypass conduit occurred during the coronary angiographic procedure when the catheter tip was located in the *saphenous vein*. In the remaining patient, however, spasm of the saphenous vein occurred in the operating room after both anastomoses had been done, and it disappeared with papaverine infusion into the graft. The degree of diameter reduction of the lumen of the saphenous vein by the spasm was severe, ranging from 50 to 100% (mean 86). The spasm of the saphenous vein (to native right in 3 patients, to native left anterior descending in 1 and to native left obtuse marginal coronary artery in 1) was associated with electrocardiographic ST-segment elevation in 2 patients, both of whom also had angina. We are surprised by the occurrence of spasm in a saphenous vein used as an aortocoronary conduit this long (≥135 days in 4 of the 6 patients) after CABG because by this time the wall of the saphenous vein has lost most of its smooth muscle cells and is more of a fibrous tube than a muscular tube.[7]

Again, we thank Drs. Lawrie and Berger for their "sharp eyes." Our own case, however, was the first in whom spasm of a saphenous vein used as a coronary conduit was demonstrated anatomically.

JESSICA M. MANN, MD
WILLIAM C. ROBERTS, MD
Bethesda, Maryland
12 May 1987

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TABLE I Clinical Data in 6 Reported Patients with Angiographically or Surgically Demonstrated Spasm of a Saphenous Vein Used as a Coronary Conduit After Aortocoronary Bypass Grafting

Case	First Author (Year)	Age (yr), Sex	Previous CA Spasm	Interval (days) CABG → C	Symptom Prompting C	Catheter in SV at Time of SV Spasm (Native CA with SV)	AP During SV Spasm	ST ↑ During SV Spasm	Percent Diameter Narrowing of SV by Spasm
1	Baduini (1981)	49, M	0	135	AP	+(R)	+	+	100
2	Victor (1981)	66, M	0	60	AP	+(LOM)	−	0	90
3	Heupler (1981)	− −	−	7	0	0	−	−	>75
4	Walinsky (1982)	66, F	+	180	AP	+(R)	+	+	100
5	Heijman (1983)	52, M	0	180	AP	+(LAD)	0	0	50
6		54, M	0	990	0	+(R)	0	0	90

AP = angina pectoris; C = catheterization; CA = coronary artery; CABG = coronary artery bypass grafting; LAD = left anterior descending; LOM = left obtuse marginal; R = right; SV = saphenous vein; + = positive or present; 0 = negative or absent; − no information available.

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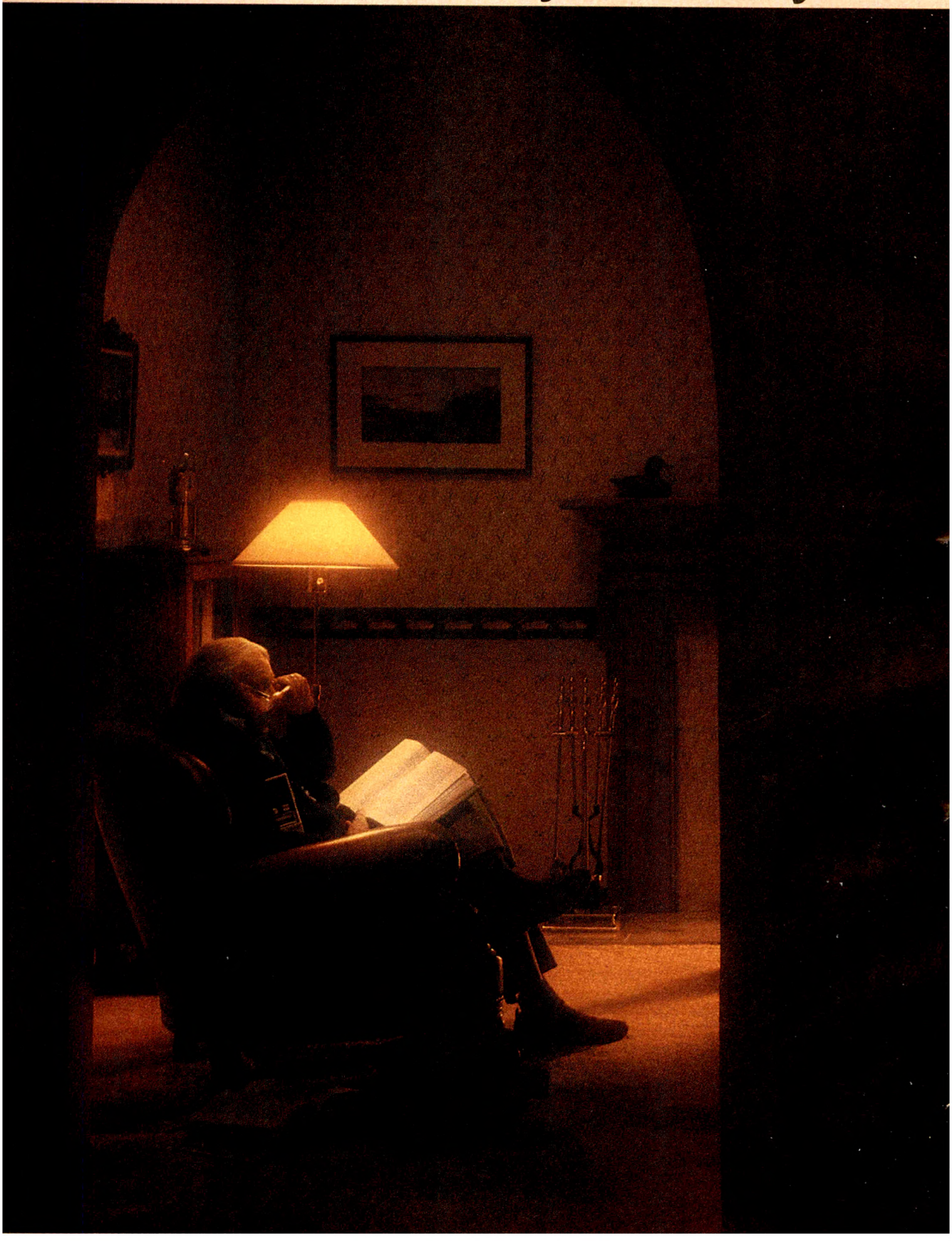

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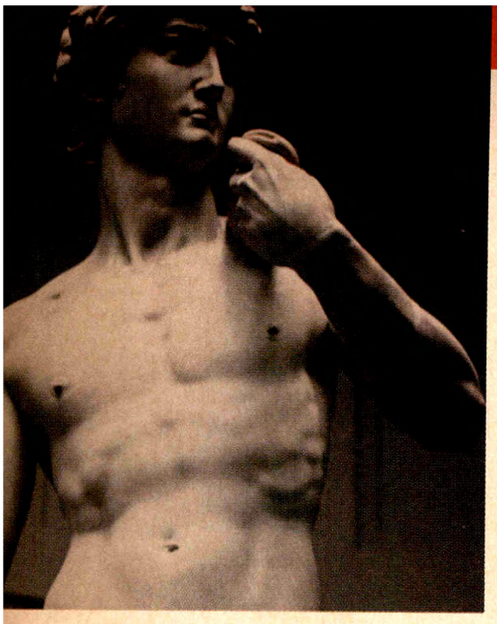

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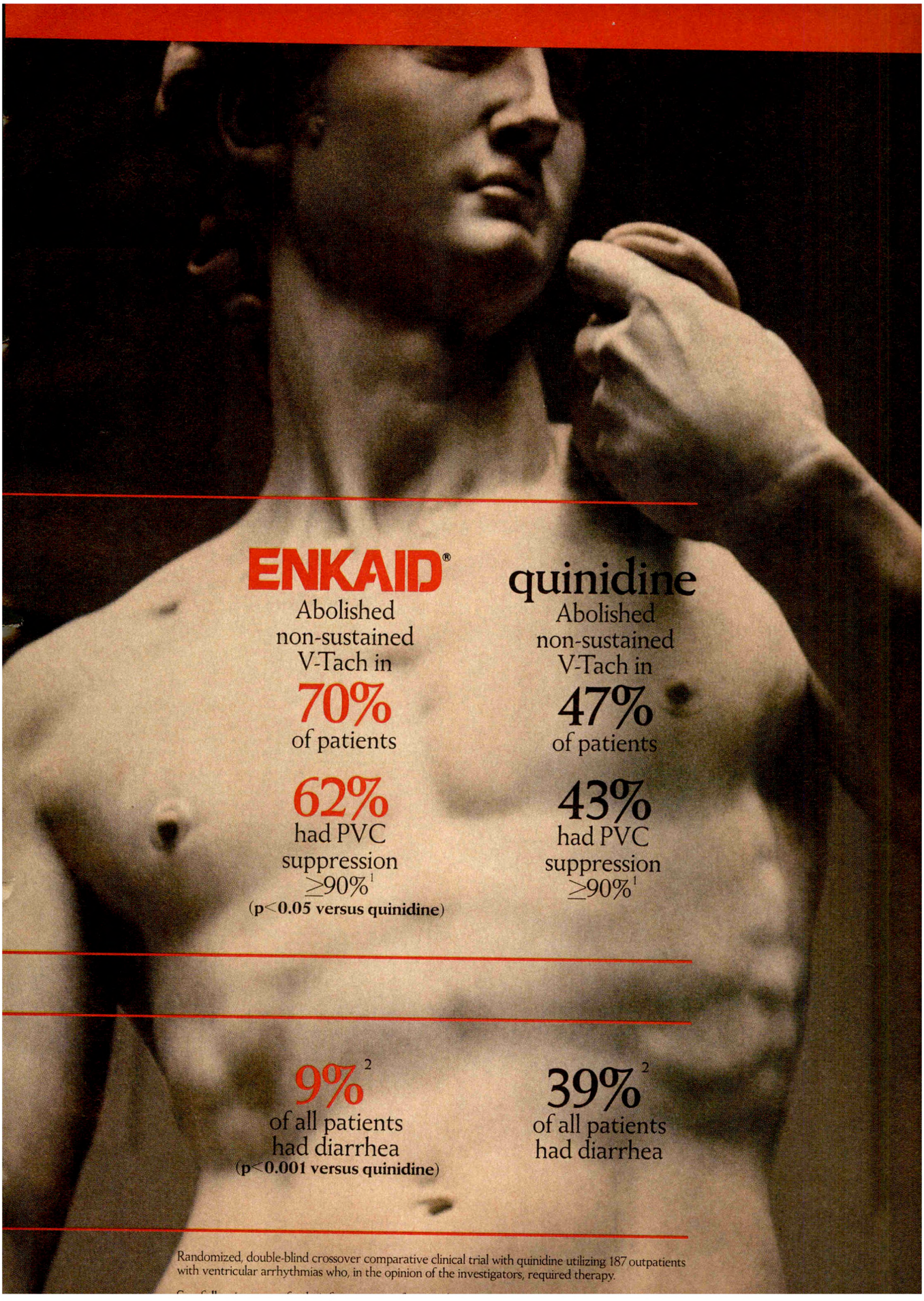
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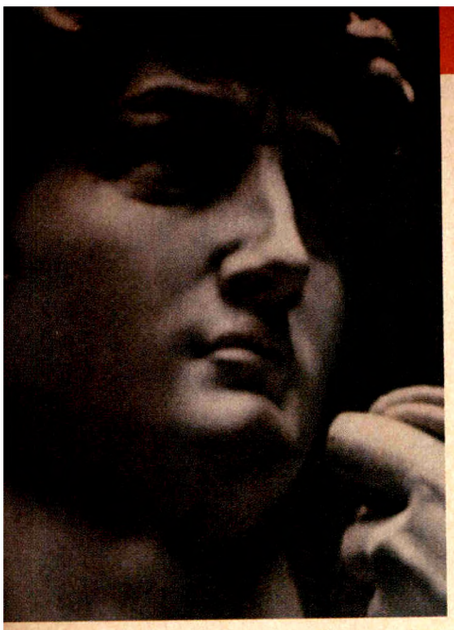
(p<0.05 versus quinidine)
9%[2]
of all patients had diarrhea
(p<0.001 versus quinidine)
quinidine
Abolished non-sustained V-Tach in
47%
of patients
43%
had PVC suppression ≥90%[1]
39%[2]
of all patients had diarrhea
Randomized, double-blind crossover comparative clinical trial with quinidine utilizing 187 outpatients with ventricular arrhythmias who, in the opinion of the investigators, required therapy.



ENKAID®
(encainide HCl)

Effective with no changes in cardiac performance

- Studies of hemodynamic effects show no changes in:
  - left ventricular ejection fraction
  - cardiac or stroke volume index
  - pulmonary capillary wedge pressure
- Effective even in patients refractory to other antiarrhythmics.

ENKAID® (encainide HCl)

Dosage	Usual Recommendation
Initial dose	25 mg t.i.d.*
First increment (if required)	35 mg t.i.d.*
Second increment (if required)	50 mg t.i.d.*
Maximum recommended	50 mg q.i.d.**

*approximately q8h **approximately q6h

Initiate therapy at lowest dosage and increase gradually. Allow 3 to 5 days between dosing increments.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

INDICATIONS AND USAGE
ENKAID is indicated for the treatment of documented life-threatening arrhythmias, such as sustained ventricular tachycardia.

ENKAID is also indicated for the treatment of patients with symptomatic non-sustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of ENKAID, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, ENKAID, like other antiarrhythmics should be initiated in the hospital. Hospitalization is also advisable for other patients with a relatively high risk of proarrhythmia including patients with symptomatic congestive heart failure, cardiomyopathy or non-sustained ventricular tachycardia, depending on their cardiac status and underlying cardiac disease. Patients should also be hospitalized at the time of a dose increase to 200 mg per day or above (see **DOSAGE AND ADMINISTRATION**).

The effects of ENKAID in patients with a recent acute myocardial infarction and in patients with supraventricular arrhythmias have not been adequately studied.

As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of ENKAID favorably affects survival or the incidence of sudden death.

CONTRAINDICATIONS
ENKAID is contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. ENKAID is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS
Proarrhythmia
ENKAID, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia; e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences.

In patients with malignant arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug induced worsening, so the following occurrence rates must be considered approximations.

Overall, in clinical trials with ENKAID about 10% of all patients had proarrhythmic events, about 6% of them representing new or worsened ventricular tachycardia. Provocation or aggravation occurred most frequently in patients who had a history of sustained ventricular tachycardia (12% of such patients), cardiomyopathy (16%), congestive heart failure (12%) or sustained ventricular tachycardia with cardiomyopathy or congestive heart failure (17%). The incidence of proarrhythmic events in patients without ventricular tachycardia or overt manifestations of clinical heart disease ranged from 3 to 4%. Proarrhythmia occurred least frequently in patients with no known structural heart disease. Age, sex, baseline ECG intervals, or ECG changes caused by ENKAID were not predictive of the occurrence of proarrhythmia.

A review of deaths in clinical trials indicates that about 1% of patients might have died of a possible proarrhythmic effect of ENKAID, virtually all of them patients with a history of ventricular tachycardia. In most cases patients had a history of sustained ventricular tachycardia or ventricular fibrillation.

Proarrhythmic events occurred most commonly during the first week of therapy and were much more common when doses exceeded 200 mg/day. Initiating therapy at 75 mg/day combined with gradual dose adjustment reduced the risk of proarrhythmia (See DOSAGE AND ADMINISTRATION).

Congestive Heart Failure
New or worsened congestive heart failure (CHF) attributed to ENKAID occurred infrequently (< 1%); nevertheless, ENKAID should be used cautiously in patients with CHF or congestive cardiomyopathy.

Electrolyte Disturbances
Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalemia should be corrected before administration of ENKAID.

Sick Sinus Syndrome—(Bradycardia-Tachycardia Syndrome)
ENKAID should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

Electrocardiographic Changes
ENKAID slows conduction and consequently produces dose related changes in the PR and QRS intervals. The intervals increase in a linear manner at doses from 30 to 225 mg/day. There is no consistent change in JT. The QTc interval is increased, but only to the extent of the increase in QRS interval.

Clinically significant changes in cardiac conduction have been observed. Sinus bradycardia, sinus pause, or sinus arrest occurred in 1% of the patients and prolongation of QRS interval to greater than/or equal to 0.20 sec developed in about 7% of the patients. The incidence of second- or third-degree AV block was less, 0.5% and 0.2% respectively.

Effects on Pacemaker Thresholds
The safety of ENKAID in patients with permanently implanted programmable pacemakers has been established in a small (10 patient) study which evaluated the effects of increasing doses on pacemaker thresholds. ENKAID has a limited potential for increasing pacemaker thresholds. Only one subject had a clinically significant change that would require pacemaker reprogramming and that occurred only at the highest dose tested (75 mg t.i.d.). These effects were reversed when the drug was discontinued. It is advisable to establish pacemaker threshold prior to encainide administration and at regular intervals during therapy. Reprogramming of multiprogrammable pacemakers may be required to increase voltage or pulse width. ENKAID should not be administered to patients with existing poor thresholds or non-programmable pacemakers unless suitable pacing rescue is available. In addition to possible rise in pacing threshold, ENKAID may suppress ventricular escape rhythms.

PRECAUTIONS
Drug Interactions
In prospective studies single and multiple doses of ENKAID have had no significant effect on serum digoxin levels. Likewise, combined digoxin/ENKAID therapy has been administered without adverse effects.

Experience has indicated no obvious problems with the combined use of ENKAID and other antiarrhythmic agents, diuretics, beta blockers or calcium channel blockers. However, because of possible additive pharmacologic effects, caution is indicated when ENKAID is used with another antiarrhythmic agent or any other drug that affects cardiac conduction.

Cimetidine (300 mg q.i.d.) increases plasma concentrations of encainide and its active metabolites. Although no clinically

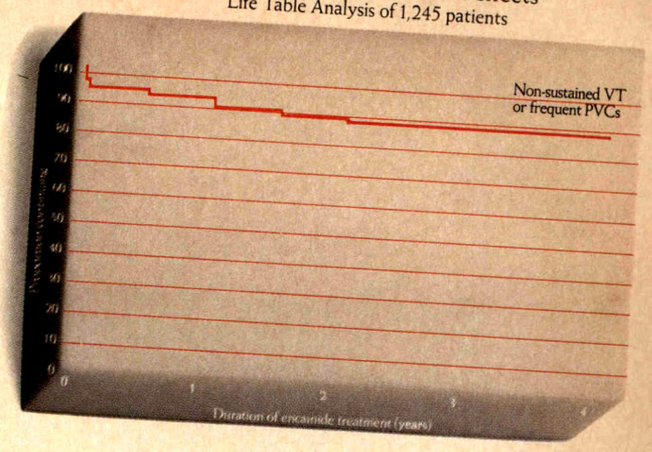
Well tolerated in long-term therapy

■ Few discontinuations due to side effects even after 4 years.

The most serious side effects of Enkaid are dizziness and blurred vision. In clinical studies with Enkaid, about 10% of patients had proarrhythmic events, occurring most frequently in patients with sustained ventricular tachycardia or underlying heart disease.

See brief summary for more information on Enkaid's side effects in life-threatening arrhythmias. Hospitalization is recommended in a facility with cardiac monitoring capabilities for patients with sustained V-Tach, sinus node dysfunction, cardiomyopathy and/or CHF, or at the time of a dose increase to 200 mg/day or above.

Discontinuations due to side effects[3]
Life Table Analysis of 1,245 patients



ENKAID® (encainide HCl)

An alternative to classic antiarrhythmic therapy

significant consequences have been reported, caution should be utilized when the two drugs are administered simultaneously. ENKAID dosage should be reduced if cimetidine is to be given to a patient taking ENKAID.

In vitro binding studies with several drugs that may be administered concomitantly have not revealed any significant alteration in the protein binding of encainide, ODE, or MODE; nor did high concentrations of encainide and its metabolites alter the binding of the other medications including such highly protein bound drugs as warfarin.

Hepatic Impairment

Patients with hepatic impairment have a significantly reduced rate of elimination of encainide, probably as a consequence of decreased metabolism to ODE and MODE; serum concentrations of ODE and MODE, however, are little altered. There is insufficient experience to be certain about the need for alterations in the dose and/or dosing interval of ENKAID in patients with hepatic disease, but it is prudent to increase doses cautiously.

Renal Impairment

Limited data suggest that reduction in the elimination of encainide and its active metabolites ODE and MODE in patients with severe renal impairment (serum creatinine >3.5 mg/dl or creatinine clearance of less than 20 ml/min) results in significant accumulation of metabolites and, to a lesser degree, encainide. In such patients therapy with ENKAID should be initiated with a single daily dose of 25 mg. If needed the dose may be increased to 25 mg b.i.d. after at least 7 days, and again to 25 mg t.i.d. after an additional 7 days if necessary. Doses above 150 mg per day are not recommended. Consideration should be given to reducing ENKAID dosage if renal function deteriorates significantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have been performed by the oral route in rats and mice at doses up to 30 mg/kg/day and 135 mg/kg/day, respectively. No drug-related increase in tumor incidence was observed. Bacterial and mammalian mutagenicity tests with encainide have been negative. No reduction in fertility occurred in rats at oral doses up to 14 mg/kg/day. Fertility was reduced when both male and female rats received oral doses of 28 mg/kg/day (approximately 13 times the average human dose) prior to mating; there was no reduction with treatment of each sex separately at the same dose.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses up to 13 and 9 times the average human dose respectively and have revealed no evidence of harm to the fetus due to encainide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Encainide is excreted in the milk of laboratory animals and has been reported to be present in human milk. Although no overt postnatal effects were observed in the postnatal phase of the rodent reproduction studies, other than decreased weight at the highest dose of 28 mg/kg/day (13 times human dose), the potential for serious adverse reactions in nursing infants from ENKAID is unknown. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of ENKAID in children less than 18 years of age have not been established.

ADVERSE REACTIONS

The most serious adverse reactions reported for ENKAID are the provocation or aggravation of ventricular arrhythmias (See **WARNINGS**). These occurred during the course of the clinical research program in about 10% of the patients who received a wide range of doses under a variety of circumstances. In some cases this resulted in the development of sustained ventricular tachycardia or ventricular fibrillation.

Only 0.4% of patients discontinued ENKAID therapy due to congestive heart failure or related causes. Second- or third-degree AV block developed in 0.5% and 0.2% of the patients respectively. Sinus bradycardia, sinus pause or sinus arrest occurred in 1% of the patients. There have been rare reports of elevated serum liver enzymes (alkaline phosphatase, serum transaminases), hepatitis, and jaundice; in which a relation to encainide is possible and there has been one instance of a rechallenge-confirmed elevation of transaminases. There have also been rare reports of elevated blood glucose levels or of increased insulin requirements in diabetic patients. Although no cause and effect relationship has been established, caution is advised in patients who develop unexplained jaundice or signs of hepatic dysfunction or hyperglycemia and consideration should be given to discontinuing therapy.

In premarketing evaluations 2400 subjects were exposed to ENKAID, of whom more than 500 were maintained on drug for two years or longer. Adverse events were sufficiently troublesome to cause discontinuation in about 7% of the patients participating in premarketing clinical trials. The most frequently reported adverse events are dizziness, blurred or abnormal vision, and headache.

The most common adverse events reported by at least 3% of patients in controlled clinical trials, occurring at frequencies greater than those seen for patients on placebo, are chest pains, death, headache, lower extremity pain, proarrhythmia, abdominal pain, constipation, diarrhea, dry mouth, dyspepsia, nausea, dizziness, insomnia, somnolence, abnormal/blurred vision, and tinnitus.

OVERDOSAGE

Intentional or accidental overdosages with ENKAID have resulted in death.

Signs, Symptoms, and Laboratory Findings Associated with an Overdosage of the Drug

Overdosage with ENKAID may produce excessive widening of the QRS complex and QT interval and AV dissociation. Hypotension, bradycardia and finally asystole may develop. A variety of conduction disturbances may be observed. Convulsions have occurred in one case of intentional overdosage.

Oral LD_{50} of the Drug in Animals

The acute, oral LD_{50} values for encainide are estimated to be 80 mg/kg in the mouse and 59 mg/kg in the rat.

Recommended General Treatment Procedures

In the event of overdosage with ENKAID patients should be hospitalized and provided with cardiac monitoring and advanced life support systems. No specific antidote for ENKAID has been identified; however, one report has suggested hypertonic sodium bicarbonate may be useful in managing the cardiac toxicity associated with an ENKAID overdosage. Acute overdosages should be treated by gastric lavage followed by activated charcoal. Treatment of overdosage should be supportive.

DOSAGE AND ADMINISTRATION

As with other antiarrhythmic agents, ENKAID therapy in patients with sustained ventricular tachycardia should be initiated in a hospital setting with facilities for cardiac rhythm monitoring. Hospitalization is also recommended for patients with sinus node dysfunction or cardiomyopathy and/or congestive heart failure even if there is no history of sustained ventricular tachycardia, and at the time of a dose increase to 200 mg per day or above.

Dosages of ENKAID should be adjusted gradually allowing 3 to 5 days between dosing increments.

HOW SUPPLIED

Capsules, 25 mg, green and yellow hard gelatin capsule imprinted with ENKAID, 25 mg, Bristol and 732.
NDC0087-0732-41 Bottles of 100.
NDC0087-0732-42 Cartons of 100 Unit Dose.
Capsules, 35 mg, green and orange hard gelatin capsule imprinted with ENKAID, 35 mg, Bristol and 734.
NDC0087-0734-41 Bottles of 100.
NDC0087-0734-42 Cartons of 100 Unit Dose.
Capsules, 50 mg, green and brown hard gelatin capsules imprinted with ENKAID, 50 mg, Bristol and 735.
NDC0087-0735-41 Bottles of 100.
NDC0087-0735-42 Cartons of 100 Unit Dose.

U.S. Pat. No. 3,931,195

References:

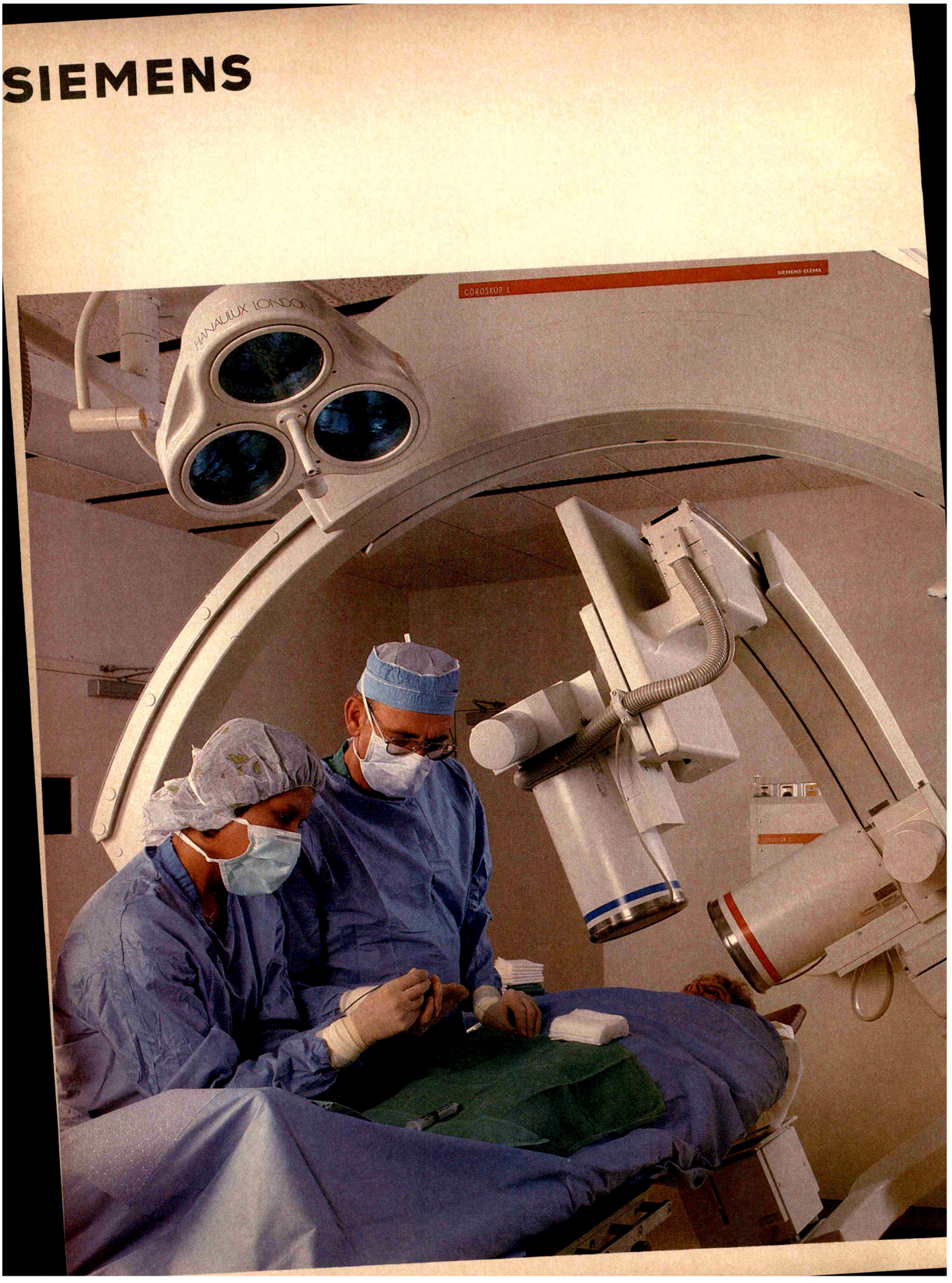
1. Rinkenberger RL, Naccarelli GV, Dougherty AH: New antiarrhythmic agents: Part X—Safety and efficacy of encainide in the treatment of ventricular arrhythmias. *Practical Cardiol* 1987;13(3):112.
2. Morganroth J, Somberg JC, Pool PE, et al: Comparative study of encainide and quinidine in the treatment of ventricular arrhythmias. *J Am Coll Cardiol* 1986;7:9-16.
3. Data on file, Bristol Laboratories.

BRISTOL LABORATORIES

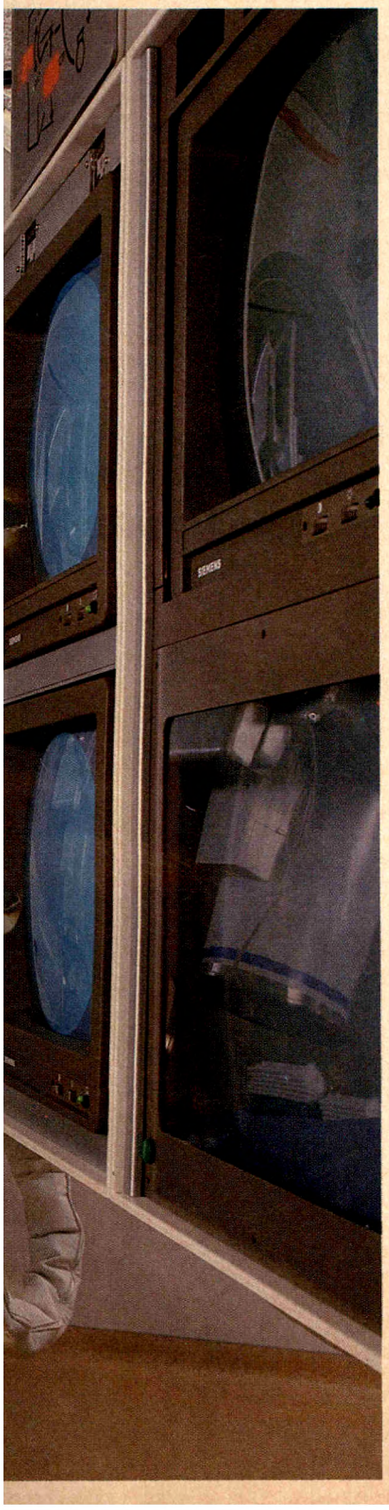
Bristol-Myers U.S. Pharmaceutical and Nutritional Group
Evansville, Indiana 47721 U.S.A.

Made in U.S.A. #B-V-20 Revised June, 1987

SIEMENS



Two independent C-arm imaging units and other design innovations provide unparalleled free access to the patient; greater positioning range and better procedural control.



The BICOR cardiovascular imaging system... Clearly better, by design.

Unrestricted patient access
BICOR® is designed to give you more working room. Nothing comes between you and your patient. Nothing interferes with your clinical technique. You never have to settle for a femoral approach when you prefer the brachial...nor compete with equipment for head-of-table space to reach a child or trauma victim. The exclusive two independent C-arm design—freedom unique to the BICOR system.

Unlimited positioning range
The BICOR exclusive dual C-arm design also gives you greater operating versatility—more options and more positioning range. Even normally difficult compound angulations like spider or four-chamber views are easily obtained. And both C-arms operate in either p.a. or lateral projections—flexibility unique to the BICOR system.

Unequalled procedural control
BICOR incorporates many practical features to promote safe, efficient use. Sensor-touch function keys and joystick drive simplify operation and training. Unobstructed, overhead digital display of angulation data lets you see exactly where you are, and exactly where you should be in followup studies. And advanced microprocesor control prevents accidental collision of imaging components or patient contact during bi-plane positioning—sophistication unique to the BICOR system.

Complete support...systems and service
BICOR innovations reflect Siemens in-depth experience in the catheterization laboratory. In addition to the BICOR, we provide other related instrumentation including systems for digital imaging; physiological monitoring; computerized data management and a full range of image recording devices.

BICOR and all Siemens systems are backed with responsive, experienced support, installation, training and service.

Siemens Medical Systems, Inc.
186 Wood Avenue South
Iselin, NJ 08830

Siemens...
technology with integrity.

MGI5010-042A WLM 408

Vaseretic®

(Enalapril Maleate-Hydrochlorothiazide|MSD)

For added hypertension control

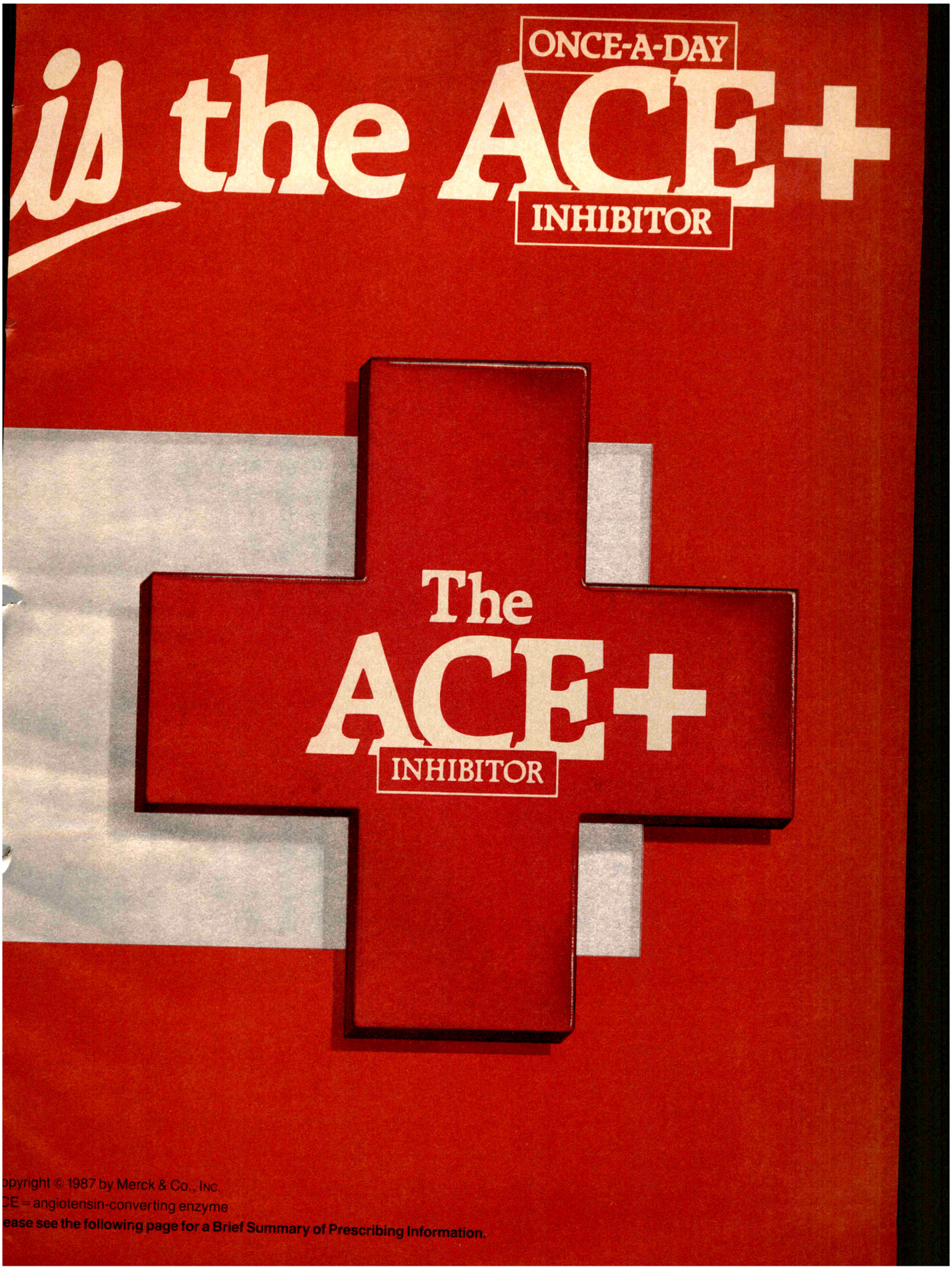
- **Hydrochlorothiazide** augments the antihypertensive effect of enalapril.
- **Enalapril** tends to reverse the potassium loss often associated with hydrochlorothiazide.
- Highly effective in adults, regardless of age or race.*

This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapri at a low initial dose (2.5 mg; see DOSAGE AND ADMINISTRATION). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

VASERETIC, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide, is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Evaluation of the hypertensive patient should always include assessment of renal function.

*Although enalapril was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalapril maleate monotherapy than non-black patients. In contrast, hydrochlorothiazide was more effective in black patients than enalapril. Concomitant administration of enalapril maleate and hydrochlorothiazide was equally effective in black and non-black patients.



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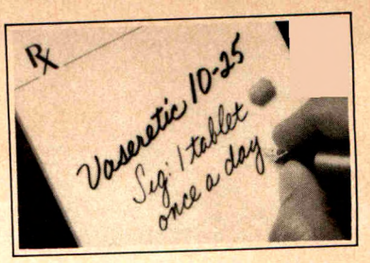
CE = angiotensin-converting enzyme

ease see the following page for a Brief Summary of Prescribing Information.

Once-A-Day
Vaseretic®
(Enalapril Maleate-Hydrochlorothiazide|MSD)



This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated, or given a diuretic and enalapril simultaneously, can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, begin enalapril at a low initial dose (see DOSAGE AND ADMINISTRATION in complete Prescribing Information). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

CONTRAINDICATIONS

VASERETIC® (Enalapril Maleate-Hydrochlorothiazide, MSD) is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. Syncope has been reported in 1.3% of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5%. The overall incidence of syncope may be reduced by proper titration of the individual components (see PRECAUTIONS, Drug Interactions; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION in complete Prescribing Information). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including enalapril. In such cases, VASERETIC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered** (see ADVERSE REACTIONS).

Neutropenia/Agranulocytosis: Another angiotensin-converting-enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions; Hydrochlorothiazide).

PRECAUTIONS

General: ***Enalapril Maleate:*** *Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting-enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.**

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with enalapril alone. In most cases, these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1%) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia (see Drug Interactions).

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: namely hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see Drug Interactions: Agents Increasing Serum Potassium).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Information for Patients: *Angioedema:* Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue and/or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC® (Enalapril Maleate-Hydrochlorothiazide, MSD) is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Enalapril Maleate:*** *Hypotension—Patients on Diuretic Therapy:* Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least one hour after the initial dose (see WARNINGS and DOSAGE AND ADMINISTRATION). *Agents Causing Renin Release:* The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics). *Other Cardiovascular Agents:* Enalapril has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions. *Agents Increasing Serum Potassium:* Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Hydrochlorothiazide: When administered concurrently, the following drugs may interact with thiazide diuretics. *Alcohol, barbiturates, or narcotics*—potentiation of orthostatic hypotension may occur. *Antidiabetic drugs (oral agents and insulin)*—dosage adjustment of the antidiabetic drug may be required. *Other antihypertensive drugs*—additive effect or potentiation. *Corticosteroids, ACTH*—intensified electrolyte depletion, particularly hypokalemia. *Pressor amines (e.g., norepinephrine)*—possible decreased response to pressor amines but not sufficient to preclude their use. *Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)*—possible increased responsiveness to the muscle relaxant. *Lithium*—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC. *Nonsteroidal anti-inflammatory drugs*—In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when VASERETIC and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Pregnancy: ***Enalapril Maleate-Hydrochlorothiazide:*** *Pregnancy Category C.* There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2-1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2-1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses; 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

There are no adequate and well-controlled studies in pregnant women. VASERETIC® (Enalapril Maleate-Hydrochlorothiazide, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. *Nonteratogenic Effects:* These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: It is not known whether enalapril is secreted in human milk, however, thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from hydrochlorothiazide, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

VASERETIC has been evaluated for safety in more than 1,500 patients, including over 300 patients treated for one year or more.

In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6%), headache (5.5%), fatigue (3.9%), and cough (3.5%). Generally, adverse experiences were mild and transient in nature.

Adverse experiences occurring in greater than 2% of patients treated with VASERETIC in controlled clinical trials are shown below:

	Percent of Patients in Controlled Studies	
	VASERETIC (n = 1,580) Incidence (discontinuation)	Placebo (n = 230) Incidence
Dizziness	8.6(0.7)	4.3
Headache	5.5(0.4)	9.1
Fatigue	3.9(0.8)	2.6
Cough	3.5(0.4)	0.9
Muscle Cramps	2.7(0.2)	0.9
Nausea	2.5(0.4)	1.7
Asthenia	2.4(0.3)	0.9
Orthostatic Effects	2.3(<0.1)	0.0
Impotence	2.2(0.5)	0.5
Diarrhea	2.1(<0.1)	1.7

Clinical adverse experiences occurring in 0.5% to 2.0% of patients in controlled trials included: *Cardiovascular:* Syncope, orthostatic hypotension, palpitations, chest pain, tachycardia. *Nervous System:* Insomnia, nervousness, paresthesia, somnolence, vertigo. *Gastrointestinal System:* Abdominal pain, vomiting, dyspepsia, constipation, flatulence, dry mouth. *Other:* Dyspnea, gout, back pain, arthralgia, hyperhidrosis, pruritus, decreased libido, rash, tinnitus, urinary tract infection. *Angioedema:* Angioedema has been reported in patients receiving VASERETIC (0.6%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately (see WARNINGS). *Hypotension:* In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9%), orthostatic hypotension (1.5%), other orthostatic effects (2.3%). In addition, syncope occurred in 1.3% of patients (see WARNINGS).

Clinical Laboratory Test Findings: *Serum Electrolytes:* See PRECAUTIONS. *Creatinine, Blood Urea Nitrogen:* In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6% of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis (see PRECAUTIONS). *Serum Uric Acid, Glucose, Magnesium, and Calcium:* See PRECAUTIONS. *Hemoglobin and Hematocrit:* Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g % and 1.0 vol %, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. *Other (Causal Relationship Unknown):* Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below: *Enalapril Maleate*—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials, adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Renal:* Renal dysfunction, renal failure, oliguria; *Hematologic:* Rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported in which a causal relationship to enalapril cannot be excluded. *Hydrochlorothiazide—Body as a Whole:* Weakness; *Digestive:* Anorexia, gastric irritation, cramping, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis; *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Special Senses:* Transient blurred vision, xanthopsia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.

HOW SUPPLIED

No. 3418—Tablets VASERETIC 10-25, are red, squared capsule-shaped, compressed tablets, coded MSD 720 on one side and VASERETIC on the other. Each tablet contains 10 mg enalapril maleate and 25 mg hydrochlorothiazide. They are supplied as follows:

NDC 0006-0720-68 bottles of 100 (with desiccant).

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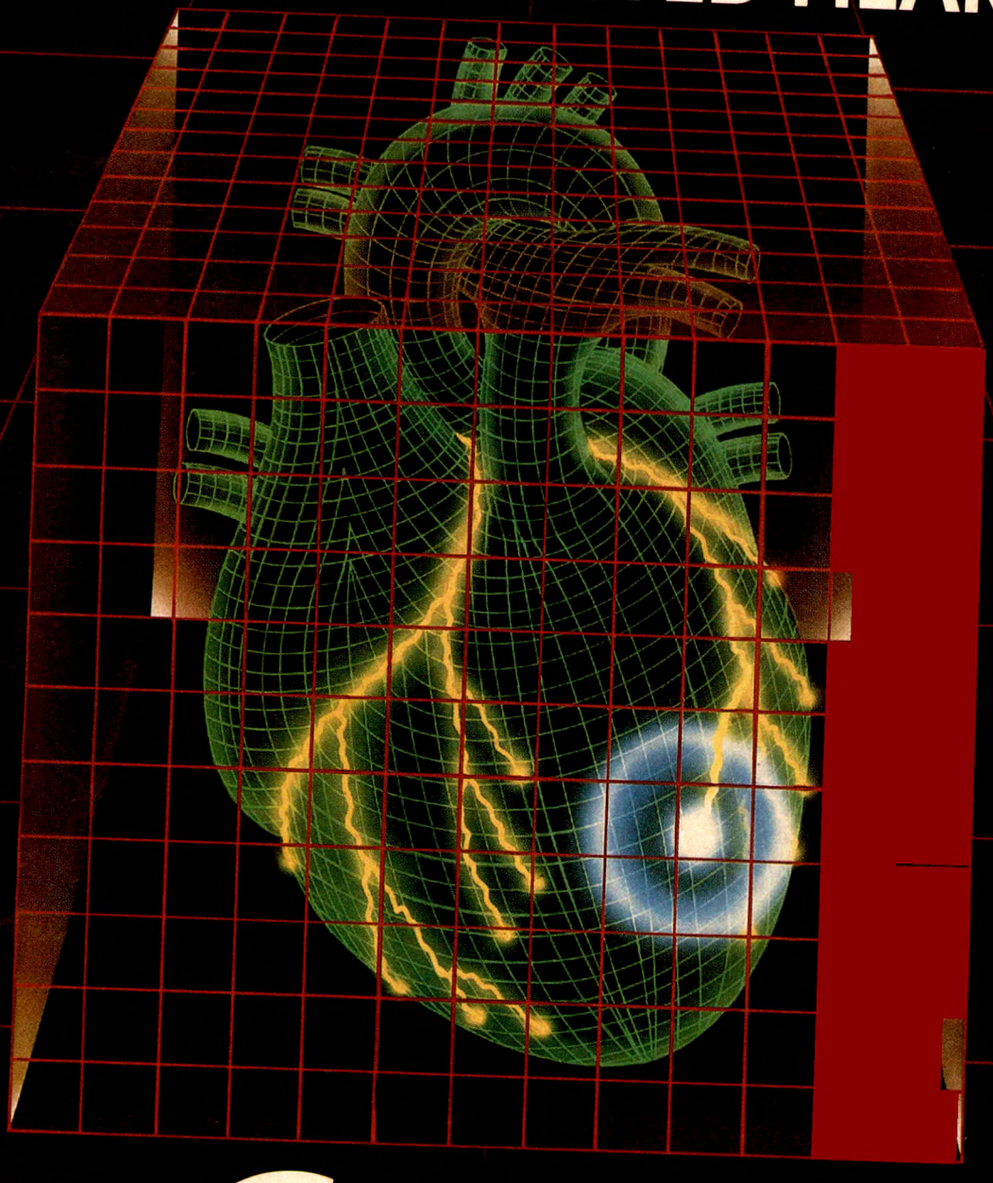

Calan® Tablets
(verapamil HCl)

Please see the adjoining page for a brief summary of the complete prescribing information.

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SEARLE

7W060T

Calan® Tablets (verapamil HCl) 120 mg 80 mg

BRIEF SUMMARY

Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure<90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes).

Warnings: Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction<30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan is used. Verapamil may occasionally produce a decrease in blood pressure below normal levels, which may result in dizziness or symptomatic hypotension. Elevations of liver enzymes have been reported. Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. The effect of verapamil on AV conduction and the SA node may cause asymptomatic 1st-degree AV block and transient bradycardia, sometimes with nodal escape rhythms. PR-interval prolongation is correlated with verapamil plasma concentrations especially during initial titration. Higher degrees of AV block are infrequent (0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Studies in a small number of patients suggest that concomitant use of Calan and oral beta-adrenergic blockers may be beneficial in certain patients with chronic stable angina or hypertension. Combined therapy can also have adverse effects on cardiac function; therefore patients should be closely monitored. A decrease in metoprolol clearance may occur with concurrent use of verapamil and metoprolol. Chronic verapamil treatment increases serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient reassessed. Verapamil used concomitantly with oral antihypertensive agents will usually have an additive effect on lowering blood pressure that in some cases may be excessive; therefore patients should be monitored appropriately. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Quinidine levels may increase during verapamil therapy. Clearance of verapamil may be reduced in concomitant use with cimetidine. Concomitant use of verapamil and lithium may result in decreased serum lithium levels. Verapamil therapy may increase carbamazepine concentrations during combined use. Therapy with rifampin may markedly reduce oral verapamil bioavailability. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Another study in rats showed no evidence of carcinogenicity. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy in children under 18 have not been established.

Adverse Reactions— oral verapamil: Constipation (8.4%), dizziness (3.5%), nausea (2.7%), hypotension (2.5%), edema (2.1%), headache (1.9%), CHF/pulmonary edema (1.8%), fatigue (1.7%), bradycardia: HR <50/min (1.4%), AV block: total 1°, 2°, 3° (1.3%)/3rd-degree (0.8%), flushing (0.1%); elevations of liver enzymes have been reported (see *Warnings*). The following reactions, reported in 1.0% or less of patients, occurred under circumstances where a causal relationship is not certain: angina pectoris, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, dyspnea, arthralgia, rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, blurred vision, gynecomastia, impotence, increased urination, spotty menstruation.

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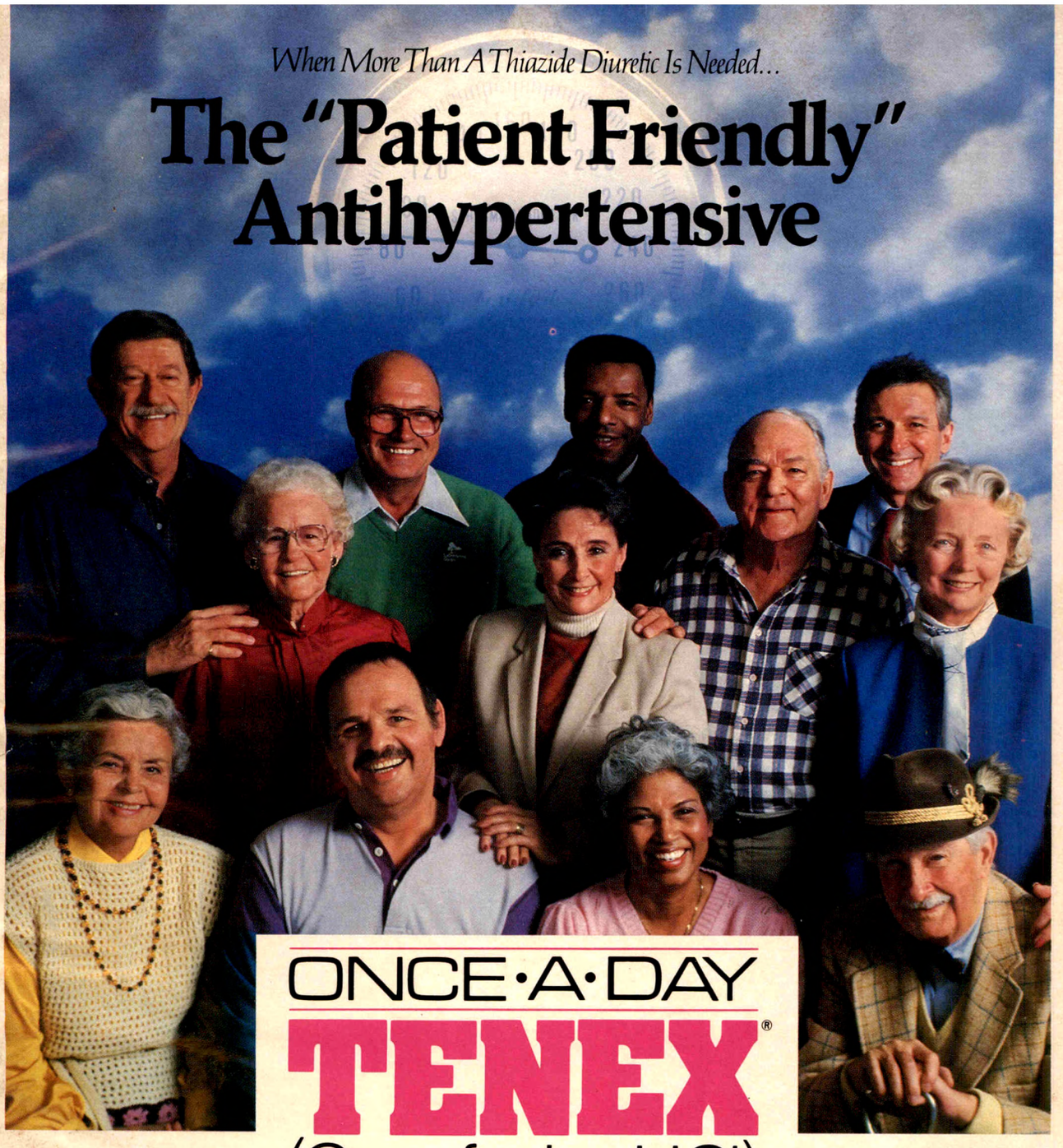

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Please see adjacent page for brief summary.

The "Patient Friendly" Antihypertensive

ONCE·A·DAY TENEX® (Guanfacine HCl)

The following is a brief summary only. Before prescribing, see complete prescribing information in Tenex product labeling.

Contraindications: Tenex is contraindicated in patients with known hypersensitivity to guanfacine hydrochloride.

Precautions: *General.* Like other antihypertensive agents, Tenex (guanfacine hydrochloride) should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal or hepatic failure.

Sedation. Tenex, like other orally active central alpha-2 adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see Adverse Reactions). When Tenex is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Rebound. Abrupt cessation of therapy with orally active central alpha-2 adrenergic agonists may be associated with increases (from depressed on-therapy levels) in plasma and urinary catecholamines, symptoms of "nervousness and anxiety" and, less commonly, increases in blood pressure to levels significantly greater than those prior to therapy.

Information for Patients. Patients who receive Tenex should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests. In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with Tenex (guanfacine hydrochloride).

Drug Interactions. No specific adverse drug interactions have been identified, but the potential for increased sedation when Tenex is given with other CNS-depressant drugs should be appreciated.

Anticoagulants. Ten patients who were stabilized on oral anticoagulants were given guanfacine, 1–2 mg/day, for 4 weeks. No changes were observed in the degree of anticoagulation.

In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, Tenex was given concomitantly with many drugs without evidence of any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihyperlipidemics (29), antigout drugs (24), oral contraceptives (18), bronchodilators (13), insulin (10), and beta blockers (10).

Drug/Laboratory Test Interactions. No laboratory test abnormalities related to the use of Tenex (guanfacine hydrochloride) have been identified.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 102 weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models guanfacine was not mutagenic.

No adverse effects were observed in fertility studies in male and female rats.

Pregnancy Category B. Administration of guanfacine to rats at 70 times the maximum recommended human dose and rabbits at 20 times the maximum recommended human dose resulted in no evidence of impaired fertility or harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery. Tenex (guanfacine hydrochloride) is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery.

Nursing Mothers. It is not known whether Tenex (guanfacine hydrochloride) is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Tenex is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

Pediatric Use. Safety and effectiveness in children under 12 years of age have not been demonstrated. Therefore, the use of Tenex in this age group is not recommended.

Adverse Reactions: Adverse reactions noted with Tenex (guanfacine hydrochloride) are similar to those of other drugs of the central α-2 adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

In a 12-week placebo-controlled, dose-response study the frequency of the most commonly observed adverse reactions showed a clear dose relationship from 0.5 to 3 mg, as follows:

Adverse Reaction	Assigned Treatment Group				
	Placebo	0.5 mg	1.0 mg	2.0 mg	3.0 mg
n =	73	72	72	72	72
Dry Mouth	5 (7%)	4 (5%)	6 (8%)	8 (11%)	20 (28%)
Somnolence	1 (1%)	3 (4%)	0 (0%)	1 (1%)	10 (14%)
Asthenia	0 (0%)	2 (3%)	0 (0%)	2 (2%)	7 (10%)
Dizziness	2 (2%)	1 (1%)	3 (4%)	6 (8%)	3 (4%)
Headache	3 (4%)	4 (3%)	3 (4%)	1 (1%)	2 (2%)
Impotence	1 (1%)	1 (1%)	0 (0%)	1 (1%)	3 (4%)
Constipation	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Fatigue	3 (3%)	2 (3%)	2 (3%)	5 (6%)	3 (4%)

There were 41 premature terminations because of adverse reactions in this study. The percent of patients who terminated and the dose at which they terminated were as follows:

Dose:	Placebo	0.5 mg	1 mg	2 mg	3 mg
Terminated:	6.9%	4.2%	3.2%	6.9%	8.3%

Reasons for dropouts among patients who received guanfacine were: somnolence, headache, weakness, dry mouth, dizziness, impotence, insomnia, constipation, syncope, urinary incontinence, conjunctivitis, paresthesia, and dermatitis.

In a second placebo-controlled study in which the dose could be adjusted upward to 3 mg per day in 1-mg increments at 3-week intervals, i.e., a setting more similar to ordinary clinical use, the most commonly recorded reactions were: dry mouth 47%, constipation 16%, fatigue 12%, somnolence 10%, asthenia 6%, dizziness 6%, headache 4%, and insomnia 4%.

Reasons for dropouts among patients who received guanfacine were: somnolence, dry mouth, dizziness, impotence, constipation, confusion, depression, and palpitations.

In the clonidine/guanfacine comparison described in Clinical Pharmacology, the most common adverse reactions noted were:

	Guanfacine (n=279)	Clonidine (n=278)
Dry mouth	30%	37%
Somnolence	21%	35%
Dizziness	11%	8%
Constipation	10%	5%
Fatigue	9%	8%
Headache	4%	4%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled trials were:

Cardiovascular—	bradycardia, palpitations, substernal pain
Gastrointestinal—	abdominal pain, diarrhea, dyspepsia, dysphagia, nausea
CNS—	amnesia, confusion, depression, insomnia, libido decrease
ENT disorders—	rhinitis, taste perversion, tinnitus
Eye disorders—	conjunctivitis, iritis, vision disturbance
Musculoskeletal—	leg cramps, hypokinesia
Respiratory—	dyspnea
Dermatologic—	dermatitis, pruritus, purpura, sweating
Urogenital—	testicular disorder, urinary incontinence
Other—	malaise, paresthesia, paresis

Adverse reaction reports tend to decrease over time. In an open-label trial of one year's duration, 580 hypertensive subjects were given guanfacine, titrated to achieve goal blood pressure, alone (51%), with diuretic (38%), with beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus vasodilator (2%). The mean daily dose of guanfacine reached was 4.7 mg.

Adverse Reaction	Incidence of adverse reactions at any time during the study	Incidence of adverse reactions at end of one year
	n = 580	n = 580
Dry mouth	60%	15%
Drowsiness	33%	6%
Dizziness	15%	1%
Constipation	14%	3%
Weakness	5%	1%
Headache	4%	0.2%
Insomnia	5%	0%

There were 52 (8.9%) dropouts due to adverse effects in this 1-year trial. The causes were: dry mouth (n = 20), weakness (n = 12), constipation (n = 7), somnolence (n = 3), nausea (n = 3), orthostatic hypotension (n = 2), insomnia (n = 1), rash (n = 1), nightmares (n = 1), headache (n = 1), and depression (n = 1).

Drug Abuse and Dependence: No reported abuse or dependence has been associated with the administration of Tenex (guanfacine hydrochloride).

Dosage and Administration: The recommended dose of Tenex (guanfacine hydrochloride) is 1 mg daily given at bedtime to minimize somnolence. Patients should already be receiving a thiazide type diuretic.

If after 3 to 4 weeks of therapy, 1 mg does not give a satisfactory result, doses of 2 and then subsequently 3 mg may be given, although most of the effect of Tenex is seen at 1 mg (see Clinical Pharmacology). Some patients may show a rise in pressure toward the end of the dosing interval; in this event a divided dose may be utilized.

Higher daily doses (rarely up to 40 mg/day, in divided doses) have been used, but adverse reactions increase significantly with doses above 3 mg/day and there is no evidence of increased efficacy. No studies have established an appropriate dose or dosing interval when Tenex (guanfacine hydrochloride) is given as the sole antihypertensive agent.

The frequency of rebound hypertension is low, but rebound can occur. When rebound occurs, it does so after 2–4 days, which is delayed compared with clonidine hydrochloride. This is consistent with the longer half-life of guanfacine. In most cases, after abrupt withdrawal of guanfacine, blood pressure returns to pretreatment levels slowly (within 2–4 days) without ill effects.

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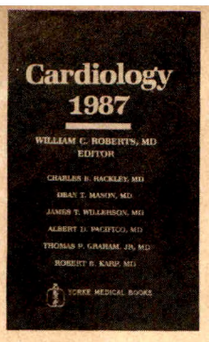

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Program Co-Chairmen: ***ERIC J. TOPOL, MD, FACC***
ROBERT M. CALIFF, MD, FACC

SATURDAY, MARCH 26, 1988
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Now that the benefits of thrombolytic therapy for acute myocardial infarction are evident, what are the practical aspects of its use? An international panel of experts at this workshop will consider the timing and safety of adjuvant mechanical interventions, the latest results from new clinical trials, and the future directions for reperfusion therapy, among other topics.

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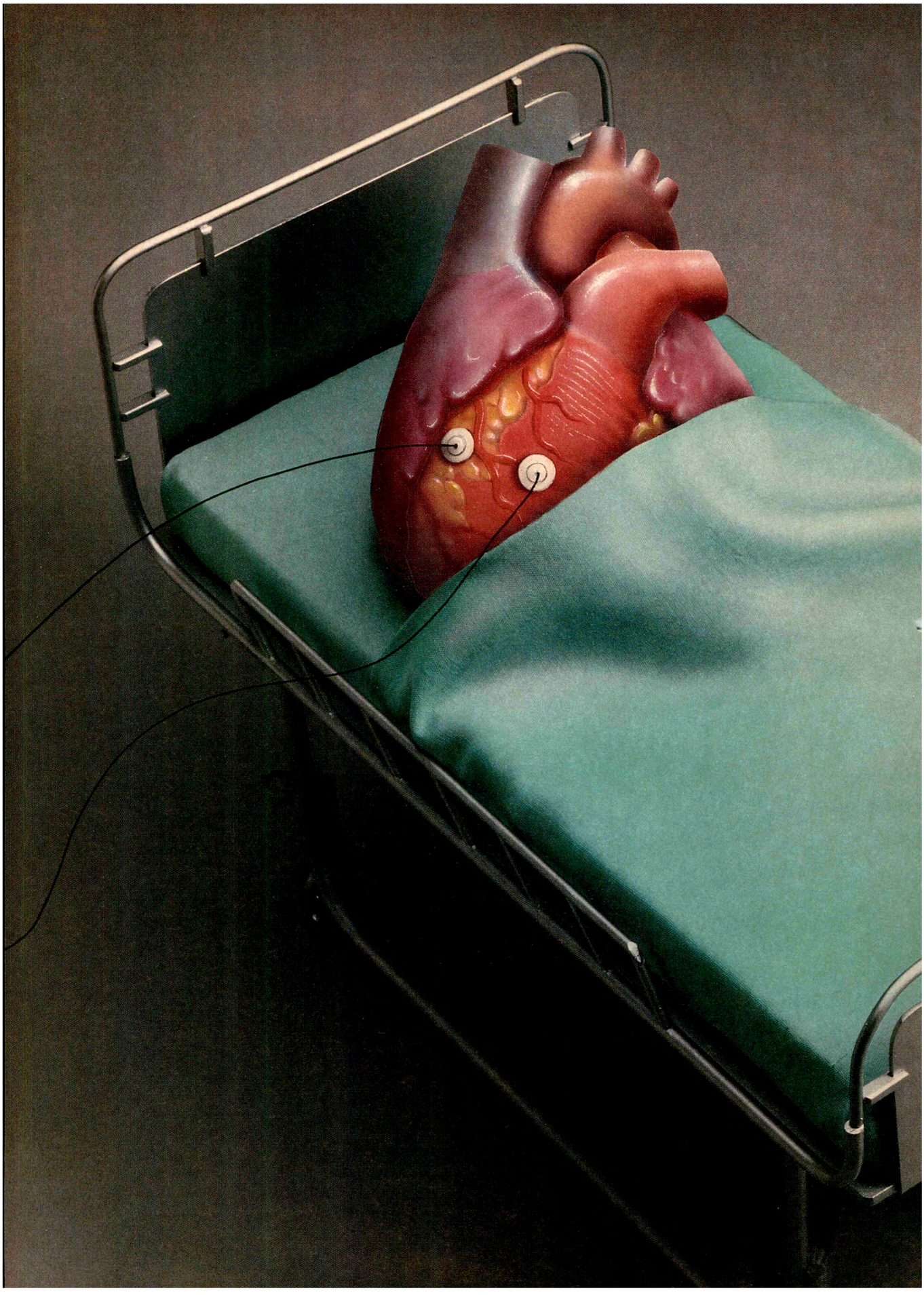

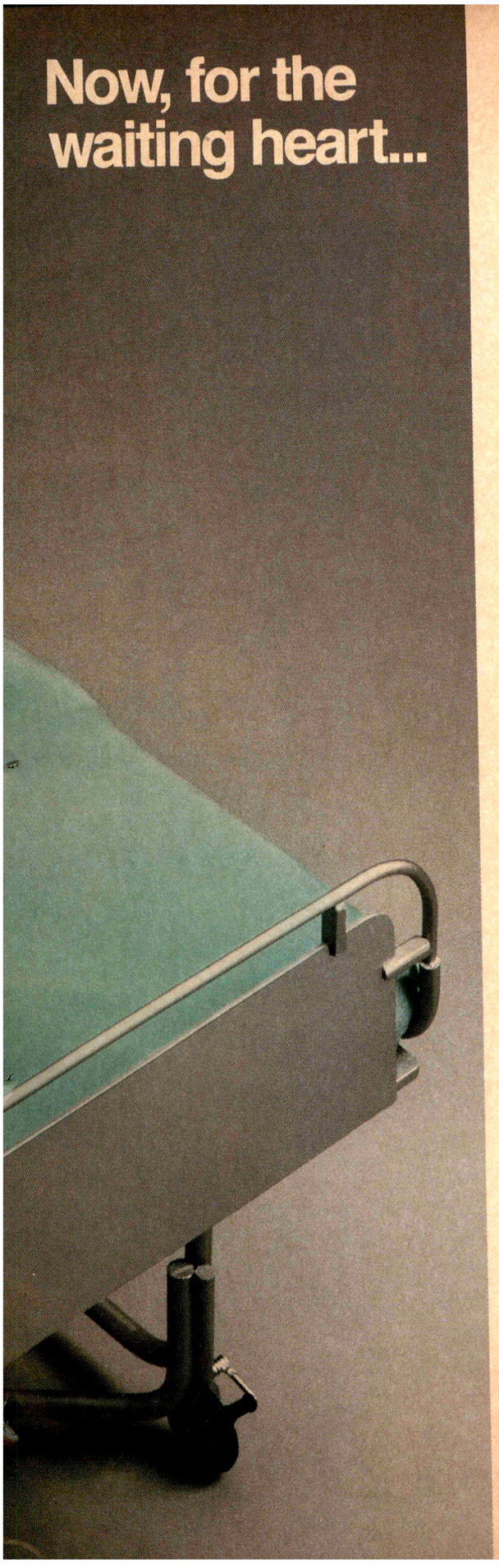

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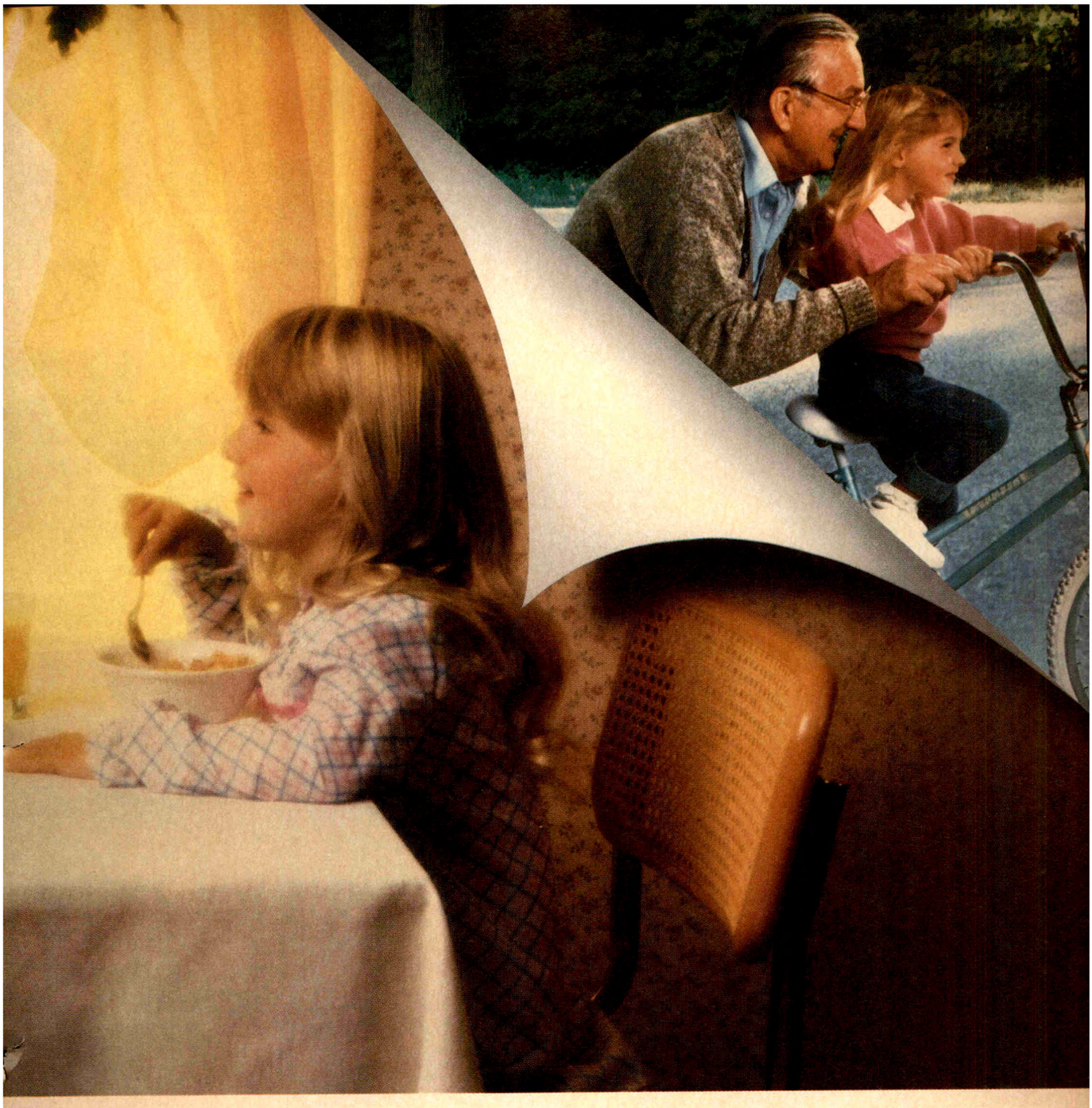

Angina attacks can occur any time: in the early morning hours, upon awakening; in the evening; or at any time during the day, triggered by exertion.

Of course, no one *plans* an angina attack. But protection *can* be planned.

CORGARD (nadolol tablets), with just a single daily dose, provides clinically proven, 24-hour protection for your patients.[1-3]

CORGARD®
(nadolol tablets)

Because no time is a good time for angina

Please see brief summary on the adjacent page.

CORGARD®
(nadolol tablets)

24-hour protection...because no time is a good time for angina

CORGARD® TABLETS
Nadolol Tablets USP

DESCRIPTION: CORGARD (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 year oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg qd; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg qd (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg qd; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg qd (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 20, 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100. The 40 mg, 80 mg, and 120 mg tablets are available in bottles of 1000 tablets. The 20 mg, 40 mg, and 80 mg tablets are also available in Unimatic® unit-dose packs of 100 tablets.

(J4-156)

References: 1. Data on file, Squibb Institute for Medical Research. 2. Vukovich RA, Foley JE, Brown B, et al: Effect of β-blockers on exercise double product (systolic blood pressure x heart rate). Br J Clin Pharmacol 7:167s-172s, 1979. 3. Kostis JB, Lacy CR, Krieger SD, et al: Atenolol, nadolol, and pindolol in angina pectoris on effort: Effect of pharmacokinetics. Am Heart J 108:1131-1136, 1984.

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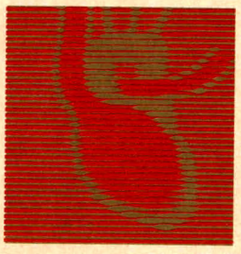

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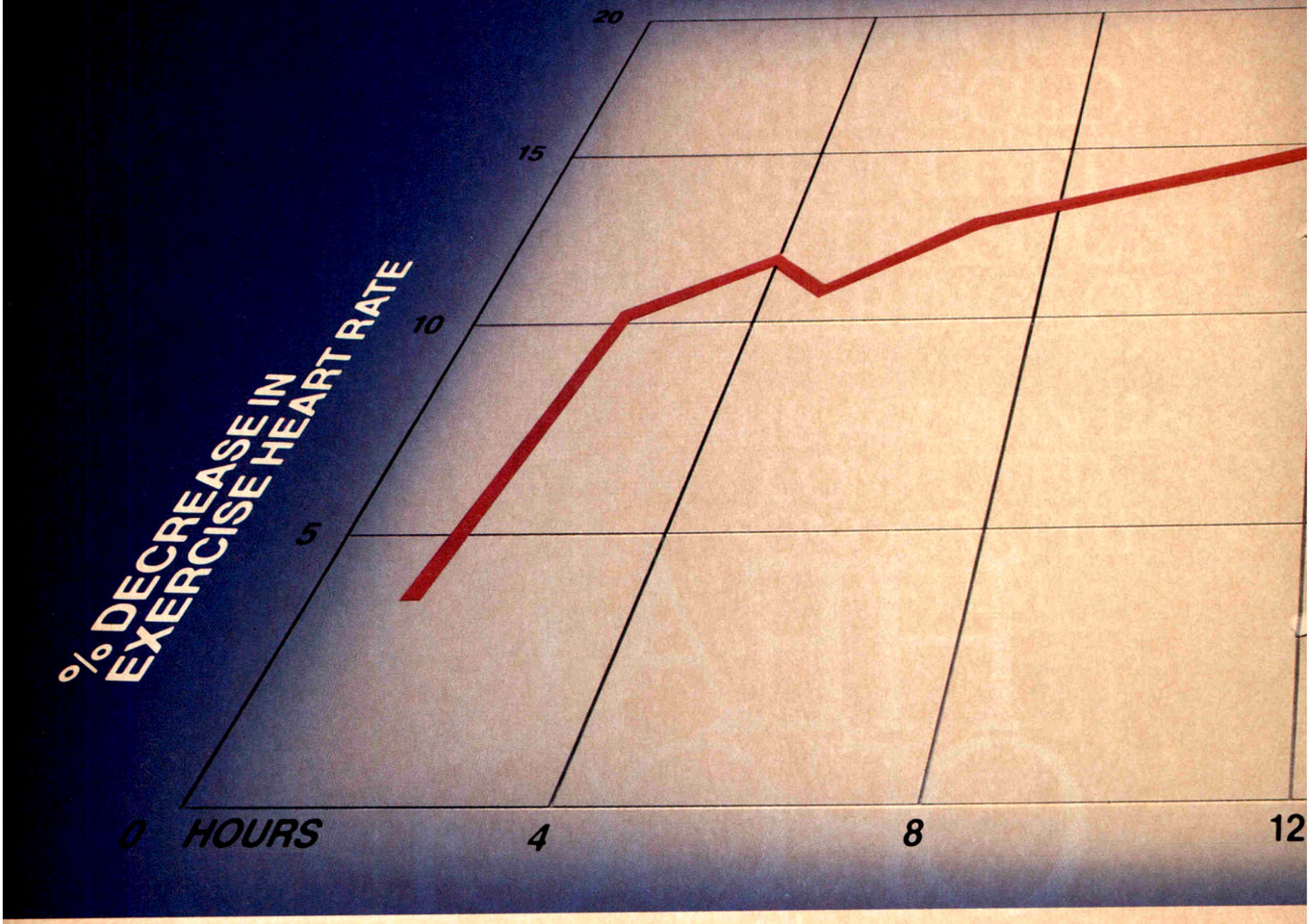
We challenge angina to



INDERAL® LA holds the line all day against angina attacks.

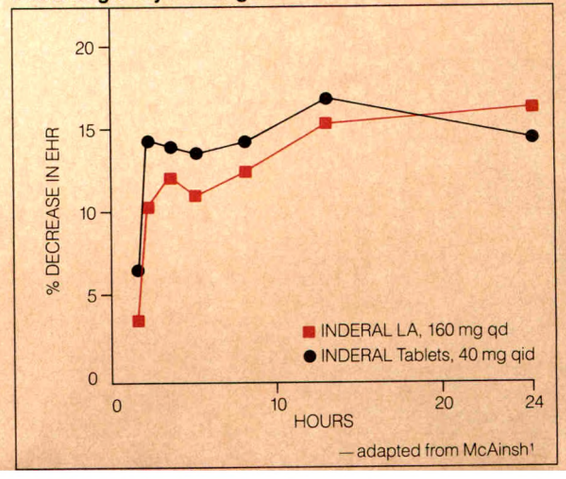
Smooth, sustained 24-hour beta blockade from a single daily dose

Periodic tests of exercise heart rate taken over 24 hours prove it. Once-daily INDERAL® LA sustains beta blockade night and day, just as well as the standard in anti-anginal therapy—qid INDERAL® (propranolol HCl) Tablets.[1]

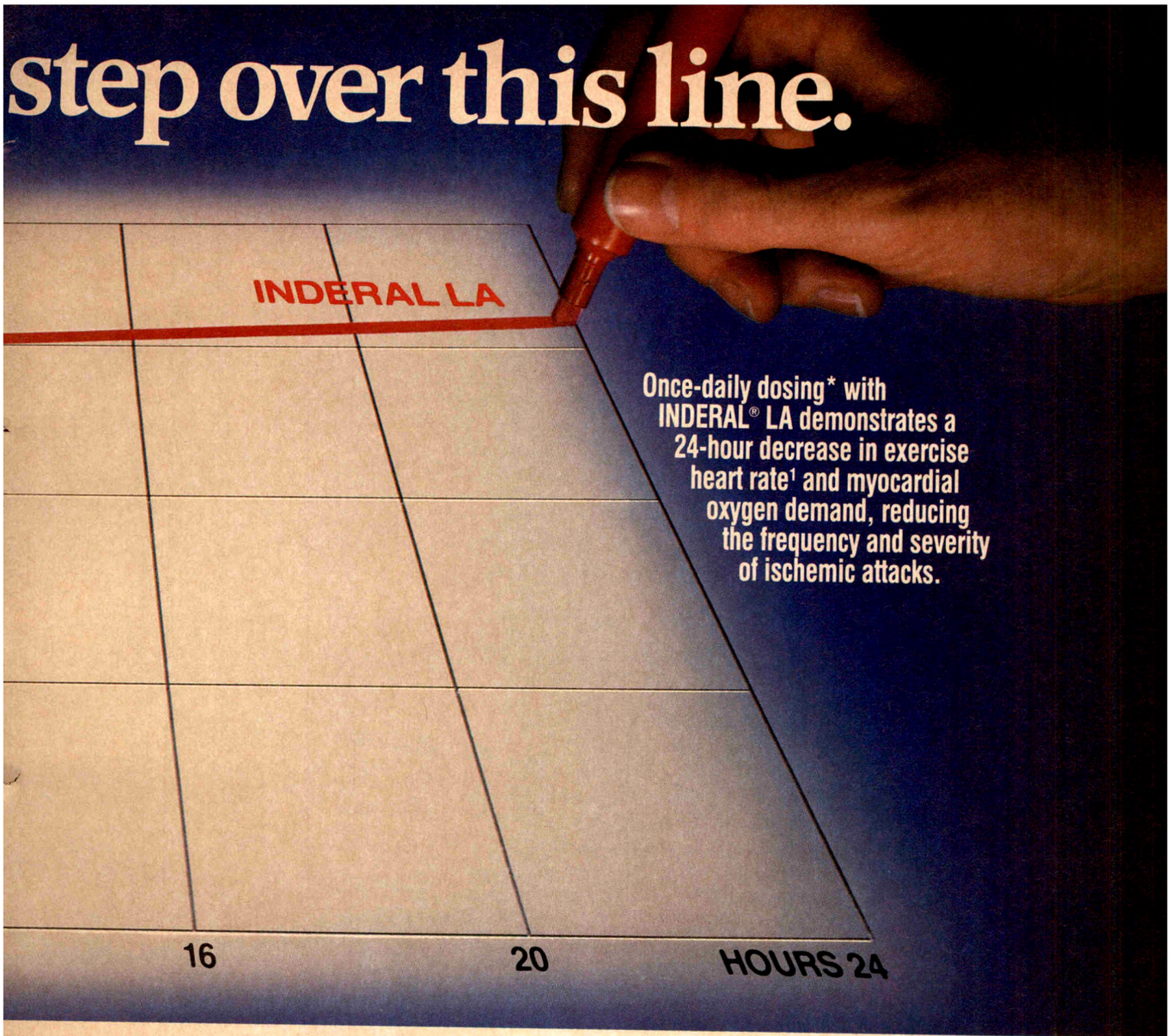
In fact, the graph demonstrates similar reductions in exercise heart rate when comparing controlled-release INDERAL® LA Capsules with divided-dose INDERAL (propranolol HCl) Tablets.[1]

The performance of INDERAL LA is also confirmed in clinical studies showing comparable reduction in the frequency and severity of angina attacks.[2,3]

Mean percentage decrease in exercise heart rate (EHR) with a single day's dosing in 12 volunteers.[1]



—adapted from McAinsh[1]



The logical complement to many other anti-anginals† in reducing symptomatic and silent ischemic episodes in unstable angina patients

As first-line therapy, INDERAL Tablets produce a favorable balance of hemodynamic effects in combination with nitrates and/or the calcium-channel blocker, nifedipine. It offsets the reflex tachycardia that concomitant vasodilator therapy can produce. Beyond that, in the presence of nitrates and nifedipine, it's been proven to reduce the number and duration of both symptomatic and silent ischemic episodes in unstable angina.[4]

Simplifying any anti-anginal regimen

Once-daily INDERAL LA helps keep a multi-drug, multi-dose, anti-anginal regimen as simple as possible. With INDERAL LA's control proven comparable to INDERAL Tablets, there's no need to postpone the convenience of once-daily dosing. *Start* your patients on INDERAL LA. And give them all the added benefits of therapy that's easy to tolerate and easy to remember to take.

ONCE-DAILY
INDERAL® LA
(PROPRANOLOL HCl) LONG ACTING CAPSULES

Holding the line all day against angina

Like conventional INDERAL Tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree, and bronchial asthma.

*When converting patients from INDERAL Tablets to INDERAL LA, start with the nearest milligram equivalent of INDERAL LA once daily. Evaluate clinical results to determine if dosage adjustment is necessary.
†The possibility of additive adverse cardiac effects mandates careful patient selection and close clinical monitoring. Please refer to respective package inserts for additional information.

Please see next page for brief summary of prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. INDERAL LA is formulated to provide a sustained release of propranolol hydrochloride. INDERAL LA is available as 60 mg, 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL Tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

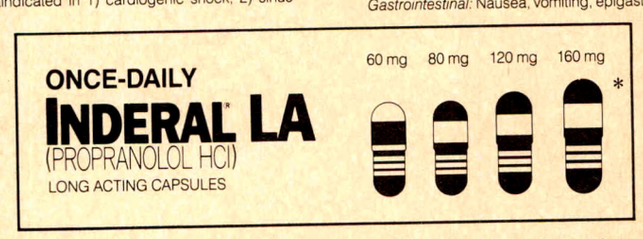
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.



WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta blockers should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid function tests, increasing T_4 and reverse T_3, and decreasing T_3.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case, this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL (propranolol HCl) is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbitone, and *rifampin* accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and *lidocaine* have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

PREGNANCY: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL Tablets to INDERAL LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg-for-mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three- to seven-day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximal dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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2R6413/1287

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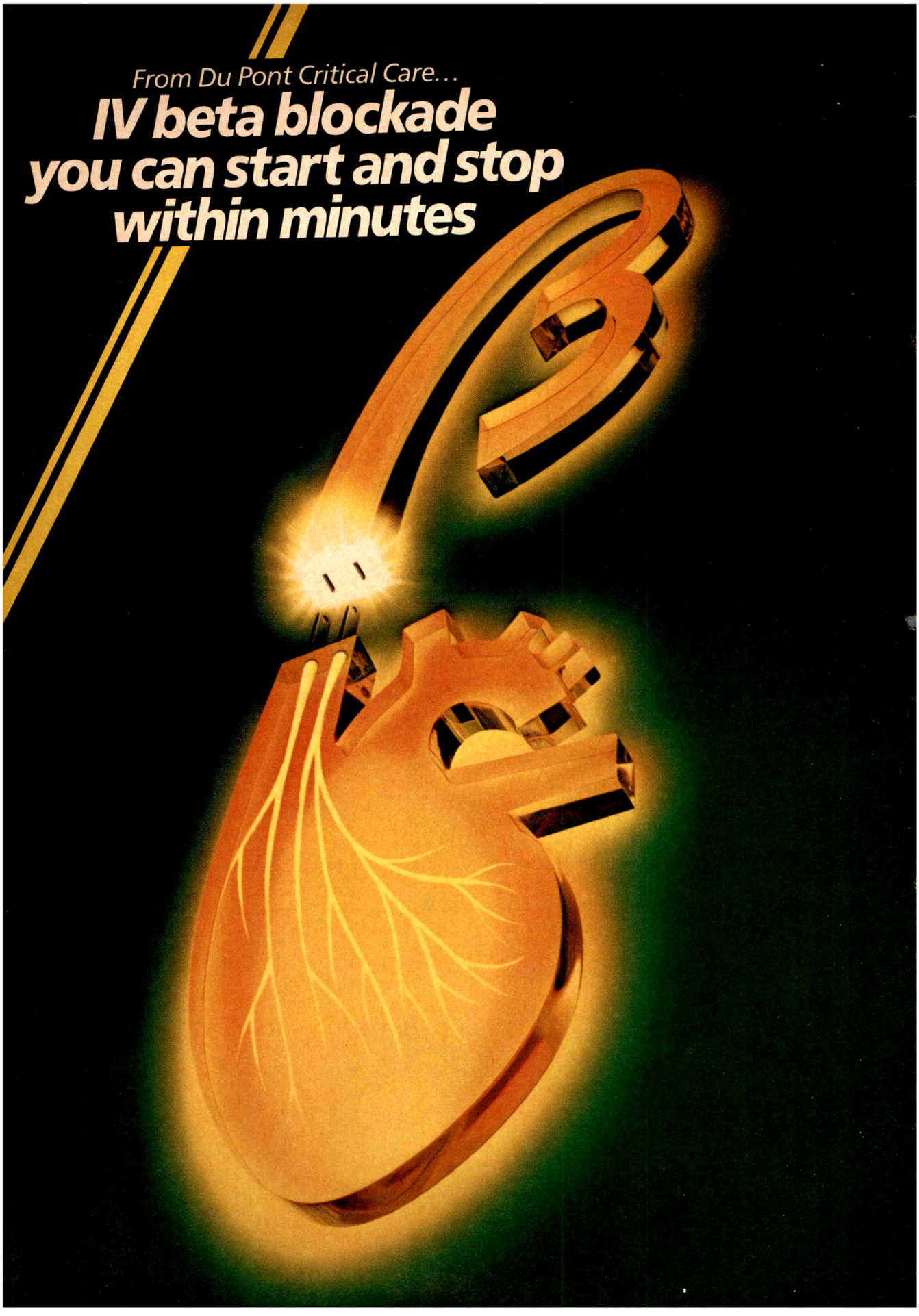


For acute control of ventricular rate...

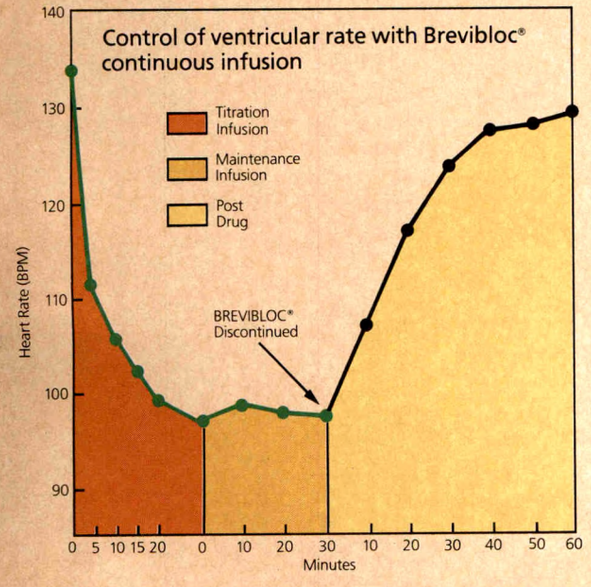
Brevibloc®
(esmolol HCl) INFUSION

Precise control

- Brevibloc® provides rapid, precise control of ventricular rate in atrial fibrillation or flutter, and in noncompensatory sinus tachycardia where, in the judgement of the physician, specific intervention is required

Rapid beta blockade, rapidly reversible

- Steady-state blood levels within 5 minutes with loading infusion [1]
- 9-minute elimination half-life allows substantial reversal of effects within 10-20 minutes of discontinuing infusion in the vast majority of patients[2-5]



Patients with atrial fibrillation/flutter titrated to dosage producing therapeutic response (50 to 300 mcg/kg/min) and continued at that dosage during maintenance period.

Adapted from Byrd RC, Sung RJ, Marks J, Parmley WW: *J Am Coll Cardiol* 1984;3(2):394.

Titratability improves control

- Administration *by continuous infusion* and 9-minute elimination half-life allow more accurate titration to meet fast-changing clinical requirements[5-8]

Safety enhanced by cardioselectivity

- Significantly less bronchospastic potential than propranolol[9]
- Unique pharmacokinetics and titratability make relative cardioselectivity clinically useful

Blood pressure reduction

- In patients with SVT, significant decreases in blood pressure occurred in 20-50% of patients. About 12% of SVT patients experienced symptomatic hypotension (mainly dizziness and diaphoresis)—6% of total discontinued[10]
- Patients—especially those with low pretreatment blood pressures—should be closely monitored during Brevibloc® administration

Please see references and brief summary of prescribing information on following page.

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Brevibloc®
A new level of control and safety in IV beta blockade

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References: 1. Data on file, Du Pont Critical Care [Steady-state blood levels]. **2.** Sum CY, et al: Kinetics of esmolol, an ultra-short-acting beta blocker, and of its major metabolite. *Clin Pharmacol Ther* 1983;34(4):427. **3.** Gold MI, et al: Heart rate and blood pressure effects of esmolol after ketamine induction and intubation. *Anesthesiology* 1986;64:718. **4.** Greenspan AM, et al: Electrophysiology of esmolol. *Am J Cardiol* 1985;56:19F. **5.** Morganroth J, et al: Comparative efficacy and tolerance of esmolol to propranolol for control of supraventricular tachyarrhythmia. *Am J Cardiol* 1985;56:33F. **6.** Abrams J, et al: Efficacy and safety of esmolol vs. propranolol in the treatment of supraventricular tachyarrhythmias—a multicenter double-blind clinical trial. *Am Heart J* 1985;110:913. **7.** Allin D, et al: Intravenous esmolol for the treatment of supraventricular tachycardia: results of a multicenter, baseline controlled safety and efficacy study in 160 patients. *Am Heart J* 1986;112:498. **8.** Byrd RC, et al: Safety and efficacy of esmolol (ASL-8052: an ultra-short acting beta adrenergic blocking agent) for control of ventricular rate in supraventricular tachycardias. *J Am Coll Cardiol* 1984;3(2):394. **9.** Sheppard D; et al: Effects of esmolol on airway function in patients with asthma. *J Clin Pharmacol* 1986;26(3):169. **10.** Data on file, Du Pont Critical Care [Hypotension].

BREVIBLOC® INJECTION (esmolol hydrochloride) 10 mL Ampul—2.5 g

Brief Summary

NOT FOR DIRECT INTRAVENOUS INJECTION. BREVIBLOC® MUST BE DILUTED PRIOR TO ITS INFUSION (SEE DOSAGE AND ADMINISTRATION SECTION).

INDICATIONS AND USAGE

Supraventricular Tachycardia

BREVIBLOC® (esmolol HCl) is indicated for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstances where short term control of ventricular rate with a short-acting agent is desirable. BREVIBLOC® is also indicated in noncompensatory sinus tachycardia where, in the physician's judgement, the rapid heart rate requires specific intervention. BREVIBLOC® is not intended for use in chronic settings where transfer to another agent is anticipated.

CONTRAINDICATIONS

BREVIBLOC® (esmolol HCl) is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock or overt heart failure (see Warnings).

WARNINGS

Hypotension: In clinical trials 20-50% of patients treated with BREVIBLOC® (esmolol HCl) have had hypotension, generally defined as systolic pressure less than 90 mmHg and/or diastolic pressure less than 50 mmHg. About 12% of the patients have been symptomatic (mainly diaphoresis or dizziness). Hypotension can occur at any dose but is dose-related so that doses beyond 200 mcg/kg/min are not recommended. Patients should be closely monitored, especially if pretreatment blood pressure is low. Decrease of dose or termination of infusion reverses hypotension, usually within 30 minutes.

Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. Continued depression of the myocardium with beta blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, the dosage should be reduced or BREVIBLOC® should be withdrawn. Although this dosage adjustment or withdrawal may be sufficient because of the short elimination half-life of BREVIBLOC®, specific treatment may also be considered. (See Overdosage.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity and titratability, BREVIBLOC® may be used with caution in patients with bronchospastic diseases. However, since $beta_1$ selectivity is not absolute, BREVIBLOC® should be carefully titrated to obtain the lowest possible effective dose. In the event of bronchospasm, the infusion should be terminated immediately; a $beta_2$ stimulating agent may be administered if conditions warrant but should be used with particular caution as patients already have rapid ventricular rates.

Diabetes Mellitus and Hypoglycemia: BREVIBLOC® should be used with caution in diabetic patients requiring a beta-blocking agent. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

PRECAUTIONS

General

Infusion concentrations of 20 mg/mL were associated with more venous irritation and thrombophlebitis than concentrations of 10 mg/mL. Concentrations greater than 10 mg/mL should, therefore, be avoided.

Because the acid metabolite of BREVIBLOC® is primarily excreted unchanged by the kidney, BREVIBLOC® (esmolol HCl) should be administered with caution to patients with impaired renal function. The elimination half-life of the acid metabolite was prolonged ten-fold and the plasma level was considerably elevated in patients with end-stage renal disease.

Drug Interactions

Catecholamine-depleting drugs, e.g., reserpine, may have an additive effect when given with beta blocking agents. Patients treated concurrently with BREVIBLOC® and a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

A study of interaction between BREVIBLOC® and warfarin showed that concomitant administration of BREVIBLOC® and warfarin does not alter warfarin plasma levels. BREVIBLOC® concentrations were equivocally higher when given with warfarin, but this is not likely to be clinically important.

When digoxin and BREVIBLOC® (esmolol HCl) were concomitantly administered intravenously to normal volunteers, there was a 10-20% increase in digoxin blood levels at some time points. Digoxin did not affect BREVIBLOC® pharmacokinetics. When intravenous morphine and BREVIBLOC® were concomitantly administered in normal subjects, no effect on morphine blood levels was seen, but BREVIBLOC® steady-state blood levels were increased by 46% in the presence of morphine. No other pharmacokinetic parameters were changed.

The effect of BREVIBLOC® on the duration of succinylcholine-induced neuromuscular blockade was studied in patients undergoing surgery. The onset of neuromuscular blockade by succinylcholine was unaffected by BREVIBLOC®, but the duration of neuromuscular blockade was prolonged from 5 minutes to 8 minutes. Although the interactions observed in these studies do not appear to be of major clinical importance, BREVIBLOC® should be titrated with caution in patients being treated concurrently with digoxin, morphine, succinylcholine or warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Because of its short term usage no carcinogenicity, mutagenicity or reproductive performance studies have been conducted with BREVIBLOC®.

Pregnancy Category C

Teratogenicity studies in rats at intravenous dosages of BREVIBLOC® up to 3000 mcg/kg/min (ten times the maximum human maintenance dosage) for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while a dosage of 10,000 mcg/kg/min produced maternal toxicity and lethality. In rabbits, intravenous dosages up to 1000 mcg/kg/min for 30 minutes daily produced no evidence of maternal toxicity, embryotoxicity or teratogenicity, while 2500 mcg/kg/min produced minimal maternal toxicity and increased fetal resorptions.

There are no adequate and well controlled studies in pregnant women. BREVIBLOC® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether BREVIBLOC® is excreted in human milk, however, caution should be exercised when BREVIBLOC® is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of BREVIBLOC® in children have not been established.

ADVERSE REACTIONS

Supraventricular Tachycardia

The following adverse reaction rates are based on use of BREVIBLOC® (esmolol HCl) in almost 400 clinical trial patients with supraventricular tachycardia. In addition, over 600 patients have been exposed in clinical studies of other conditions. The most important adverse effect has been hypotension (see Warnings). Most adverse effects have been mild and transient.

Cardiovascular—Symptomatic hypotension (diaphoresis, dizziness) occurred in 12% of patients, and therapy was discontinued in about 11%, about half of whom were symptomatic. Asymptomatic hypotension occurred in about 25% of patients. Hypotension resolved during BREVIBLOC® infusion in 63% of these patients and within 30 minutes after discontinuation of infusion in 80% of the remaining patients. Diaphoresis accompanied hypotension in 10% of patients. Peripheral ischemia occurred in approximately 1% of patients. Pallor, flushing, bradycardia (heart rate less than 50 beats per minute), chest pain, syncope, pulmonary edema and heart block have each been reported in less than 1% of patients. In two patients without supraventricular tachycardia but with serious coronary artery disease (post inferior myocardial infarction or unstable angina), severe bradycardia/sinus pause/asystole has developed, reversible in both cases with discontinuation of treatment.

Central Nervous System—Dizziness has occurred in 3% of patients; somnolence in 3%, confusion, headache, and agitation in about 2%, and fatigue in about 1% of patients. Paresthesia, asthenia, depression, abnormal thinking, anxiety, anorexia, and lightheadedness were reported in less than 1% of patients. One brief (30 second) episode of grand mal seizure has been reported.

Respiratory—Bronchospasm, wheezing, dyspnea, nasal congestion, rhonchi, and rales have each been reported in less than 1% of patients.

Gastrointestinal—Nausea was reported in 7% of patients. Vomiting has occurred in about 1% of patients. Dyspepsia, constipation, dry mouth, and abdominal discomfort have each occurred in less than 1% of patients. Taste perversion has also been reported.

Skin (Infusion Site)—Infusion site reactions including inflammation and induration were reported in about 8% of patients. Edema, erythema, skin discoloration, and burning at the infusion site have each occurred in less than 1% of patients.

Miscellaneous—Each of the following has been reported in less than 1% of patients: Urinary retention, speech disorder, abnormal vision, midscapular pain, rigors, and fever.

OVERDOSAGE

Acute Toxicity

A single case of accidental overdosage with BREVIBLOC® (esmolol HCl) has occurred to date. A 5000 mcg/kg/min dose of BREVIBLOC® instead of the recommended 500 mcg/kg/min loading dose, was administered over one minute to a patient with atrial flutter. Immediately following the infusion, marked decreases in heart rate and blood pressure were observed and the patient became drowsy but could be aroused. The infusion rate of BREVIBLOC® was decreased to 5 mcg/kg/min and over the next eight minutes the patient's rhythm converted to normal sinus rhythm and the patient started feeling better. Hypotension persisted for a period of four minutes after decreasing the dosage of BREVIBLOC®. The drowsiness disappeared 15 minutes following discontinuation of BREVIBLOC®.

Because of its approximately 9-minute elimination half-life, the first step in the event of toxicity should be to discontinue BREVIBLOC® administration. Then, based on the pharmacologic actions, the following general measures should also be considered:

Bradycardia: Intravenous administration of atropine or another anticholinergic drug.

Bronchospasm: Intravenous administration of a $beta_2$ stimulating agent and/or a theophylline derivative.

Cardiac Failure: Intravenous administration of a diuretic and/or digitalis glycoside. In shock resulting from inadequate cardiac contractility, intravenous administration of dopamine, dobutamine, isoproterenol, or amrinone may be considered.

DOSAGE AND ADMINISTRATION

NOT FOR DIRECT INTRAVENOUS INJECTION. BREVIBLOC® IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED PRIOR TO ITS INFUSION. BREVIBLOC® SHOULD NOT BE ADMIXED WITH SODIUM BICARBONATE. BREVIBLOC® SHOULD NOT BE MIXED WITH OTHER DRUGS PRIOR TO DILUTION IN A SUITABLE INTRAVENOUS FLUID.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Dilution: Aseptically remove 20 mL from a 500-mL bottle of one of the intravenous fluids (refer to full prescribing information for compatibility with commonly used intravenous fluids) and add the contents of two (2) ampuls of BREVIBLOC® (each containing 2.5 g esmolol hydrochloride). This yields a final concentration of 10 mg/mL. The diluted solution is stable for at least 24 hours at room temperature. Note: Concentrations of BREVIBLOC® greater than 10 mg/mL are likely to produce irritation on continued infusion (see Precautions). BREVIBLOC® has, however, been well tolerated when administered via a central vein.

Supraventricular Tachycardia

In the treatment of supraventricular tachycardia, responses to BREVIBLOC® usually (over 95%) occur within the range of 50 to 200 mcg/kg/min. The average effective dosage is approximately 100 mcg/kg/min although dosages as low as 25 mcg/kg/min have been adequate in some patients. Dosages as high as 300 mcg/kg/min have been used, but these provide little added effect and an increased rate of adverse effects, and are not recommended. Dosage of BREVIBLOC® in supraventricular tachycardia must be individualized by titration in which each step consists of a loading dosage followed by a maintenance dosage.

To initiate treatment of a patient with supraventricular tachycardia, administer a loading dosage infusion of 500 mcg/kg/min of BREVIBLOC® for one minute followed by a 4 min maintenance infusion of 50 mcg/kg/min. If an adequate therapeutic effect is not observed within five minutes, repeat the same loading dosage and follow with a maintenance infusion increased to 100 mcg/kg/min.

Continue titration procedure as above, repeating loading infusion (500 mcg/kg/min for 1 minute), increasing maintenance infusion by increments of 50 mcg/kg/min (for 4 minutes). As the desired heart rate or a safety end-point (e.g., lowered blood pressure) is approached, omit the loading infusion and reduce incremental dose in maintenance infusion from 50 mcg/kg/min to 25 mcg/kg/min or lower. Also, if desired, increase interval between titration steps from 5 to 10 minutes.

This specific dosage and administration regimen has not been studied intraoperatively and because of the time required for titration, may not be optimal for intraoperative use.

Maintenance dosages above 200 mcg/kg/min have not been shown to have significantly increased benefits, and the safety of dosages above 300 mcg/kg/min has not been studied.

In the event of an adverse reaction, the dosage of BREVIBLOC® may be reduced or discontinued. If a local infusion site reaction develops, an alternative infusion site should be used. The use of butterfly needles should be avoided.

Abrupt cessation of BREVIBLOC® in patients has not been reported to produce the withdrawal effects which may occur with abrupt withdrawal of beta-blockers following chronic use in coronary artery disease (CAD) patients. However, caution should still be used in abruptly discontinuing infusions of BREVIBLOC® in CAD patients.

After achieving an adequate control of the heart rate and a stable clinical status in patients with supraventricular tachycardia, transition to alternative antiarrhythmic agents such as propranolol, digoxin, or verapamil, may be accomplished.

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January, 1987 A43004 AMC-0206

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- ☐ **It's acceptable vs liquids**—greater palatability, fewer GI complaints, lower incidence of nausea[2]
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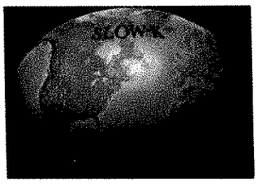

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†Pooled mean serum potassium following oral administration of 30 mEq K-Tab compared to 24 mEq Slow-K in diuretic-treated hypertensives (n = 20) over 8 weeks.

C I B A

References: 1. Data on file, CIBA Pharmaceutical Company. 2. Skoutakis VA, Acchiardo SR, Wojciechowski NJ, et al: Liquid and solid potassium chloride: Bioavailability and safety. *Pharmacotherapy* 1980;4(6):392-397. 3. Skoutakis VA, Carter CA, Acchiardo SR: Therapeutic assessment of Slow-K and K-Tab potassium chloride formulations in hypertensive patients treated with thiazide diuretics. *Drug Intell Clin Pharm* 1987;21:436-440.

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potassium chloride USP
Slow-Release Tablets
8 mEq (600 mg)

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION SEE PACKAGE INSERT)

INDICATIONS AND USAGE
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.
1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy; and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
Potassium supplements are contraindicated in patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene) (see OVERDOSAGE).

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation. Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.

WARNINGS
Hyperkalemia (See OVERDOSAGE).
In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.

The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction With Potassium-Sparing Diuretics
Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions
Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis
Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
General:
The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium.

Information for Patients
Physicians should consider reminding the patient of the following:
To take each dose without crushing, chewing, or sucking the tablets.
To take this medicine only as directed. This is especially important if the patient is also taking both diuretics and digitalis preparations.
To check with the physician if there is trouble swallowing tablets or if the tablets seem to stick in the throat.
To check with the doctor at once if tarry stools or other evidence of gastrointestinal bleeding is noticed.

Laboratory Tests
Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions
Potassium-sparing diuretics: see WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C
Animal reproduction studies have not been conducted with Slow-K. It is also not known whether Slow-K can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Slow-K should be given to a pregnant woman only if clearly needed.

Nursing Mothers
The normal potassium ion content of human milk is about 13 mEq/L. It is not known if Slow-K has an effect on this content. Caution should be exercised when Slow-K is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
One of the most severe adverse effects is hyperkalemia (see CONTRAINDICATIONS, WARNINGS, and OVERDOSAGE). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see CONTRAINDICATIONS and WARNINGS); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE
The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see CONTRAINDICATIONS and WARNINGS). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration (6.5-8.0 mEq/L) and characteristic electrocardiographic changes (peaking of T waves, loss of P wave, depression of S-T segment, and prolongation of the Q-T interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest (9-12 mEq/L).

Treatment measures for hyperkalemia include the following: (1) elimination of foods and medications containing potassium and of potassium-sparing diuretics; (2) intravenous administration of 300-500 ml/hr of 10% dextrose solution containing 10-20 units of insulin per 1,000 ml; (3) correction of acidosis, if present, with intravenous sodium bicarbonate; (4) use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

DOSAGE AND ADMINISTRATION
The usual dietary intake of potassium by the average adult is 40-80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq or more per day for the treatment of potassium depletion. Large numbers of tablets should be given in divided doses.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed, chewed, or sucked.

HOW SUPPLIED
Tablets—600 mg of potassium chloride (equivalent to 8 mEq) round, buff colored, sugar-coated (imprinted Slow-K)

Bottles of 100	NDC 0083-0165-30
Bottles of 1000	NDC 0083-0165-40
Consumer Pack—One Unit	
12 Bottles—100 tablets each	NDC 0083-0165-65
Accu-Pak® Unit Dose (Blister pack)	
Box of 100 (strips of 10)	NDC 0083-0165-32

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*Based on worldwide sales data on file, CIBA Pharmaceutical Company.
Capsule or tablet slow-release potassium chloride preparations should be reserved for patients who cannot tolerate, refuse to take, or have compliance problems with liquid or effervescent potassium preparations because of reports of intestinal and gastric ulceration and bleeding with slow-release KCl preparations.

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MARCH 25, 1988

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The American Journal of CARDIOLOGY®

A Symposium: Advances in Clinical Practice of Nitrate Therapy

Editors:
Adam Schneeweiss, MD
Marija Weiss, DSc

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A Symposium: Advances in Clinical Practice of Nitrate Therapy

Editors:
Adam Schneeweiss, MD
Director
The Geriatric Cardiology Research Foundation
Tel Aviv, Israel

Marija Weiss, DSc
Head
Medical Department International
Schwarz Pharma
Monheim, F.R.G.

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MARCH 25, 1988

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A Symposium: Advances in Clinical Practice of Nitrate Therapy

Introduction

ADAM SCHNEEWEISS, MD, and MARIJA WEISS, DSc

About 10 years ago it was believed that only little more might be said on nitrate therapy. After 100 years of use, nitrates appeared to offer many well-known therapeutic advantages, but no lines for further research. Over the last decade, however, we have observed the following new and exciting developments in the field, which change the profile of nitrate therapy and provide new and important therapeutic tools:

1. New indications for nitrates, including prevention (preferable to treatment) of all forms of angina pectoris and silent ischemia, treatment of myocardial infarction, congestive heart failure, perioperative cardiovascular complications and various extracardiac indications.

From Schwarz GmbH, Monheim, Federal Republic of Germany.

2. Development of molecules with relative selectivity to various segments of the circulation, such as isosorbide-5-mononitrate, which appears to be relatively selective for the venous circulation.

3. Development of new drug delivery systems. Isosorbide dinitrate spray and nitroglycerin spray were shown to be superior to sublingual tablets in rapidity of effect in treatment of angina pectoris, pulmonary edema and congestive heart failure. Transdermal nitroglycerin patches allow long-term treatment of congestive heart failure and angina pectoris. Long-acting oral formulations of nitrates simplify some traditional and complex therapeutic regimens.

This symposium on advances in the clinical practice of nitrate therapy will discuss some of these achievements.

More Rapid Relief of Pain with Isosorbide Dinitrate Oral Spray than with Sublingual Tablets in Elderly Patients with Angina Pectoris

LEONARDO H. REISIN, MD, ELIAHU LANDAU, MD, and AZIZ DARAWSHI, MD

To evaluate the possibility of improving clinical practice in the treatment of angina pectoris, the duration of relief of pain with isosorbide dinitrate (ISDN) oral spray and sublingual tablets were compared in elderly patients with chronic stable angina pectoris. Nine patients (mean age 67 years) were studied in a randomized crossover trial. The patients underwent bicycle ergometry, which resulted in typical chest pain associated with electrocardiographic ST-segment depression in all 9. The patients received ISDN oral spray or sublingual tablets immediately on termination of exercise. At least 6 hours later another ergometry test was performed and the patients were crossed over to the other drug. ISDN spray relieved pain in all patients at a mean duration of 61.6 ± 24.4 seconds after administration, whereas the duration of relief of pain by ISDN sublingual tablets was 112.4 ± 70 seconds. The difference was highly significant ($p < 0.0005$). It is concluded that clinical practice of treatment of angina pectoris in the elderly can be improved by using ISDN oral spray rather than sublingual tablets. The spray is effective at twice the rapidity of the sublingual tablet. (Am J Cardiol 1988;61:2E–3E)

Nitrates are used for relief and prevention of pain in patients with angina pectoris.[1–4] The most rapid conventional therapy for relief of pain in patients with exercise-induced angina pectoris is sublingual administration of nitrates in tablet form. The rapidity of action is important because until relief, the patients have myocardial ischemia as seen by electrocardiographic ST-segment depression. However, even the rapidly acting sublingual tablets take a few minutes before onset of effect. Peak plasma levels of nitrates are achieved about 2 minutes after dissolution of the tablet.[5] Moreover, the time required for dissolution of the tablet (which varies from patient to patient) further delays the onset of action. In elderly patients this delay may be more pronounced because dryness of the mouth (more often a problem in the elderly than in the young) impairs tablet dissolution.[6]

Isosorbide dinitrate (ISDN) oral spray theoretically should act more rapidly than sublingual tablets because no time is required for dissolution of a tablet. In this study we compared the rapidity of pain relief by ISDN oral spray and sublingual tablets in the elderly.

From the Cardiology Department, Barzilai Hospital, Ashkelon, Israel.

Address for reprints: Adam Schneeweiss, MD, Geriatric Cardiology Research Foundation, 9 Kehilat Sofia Street, 69018 Tel Aviv, Israel.

Methods

Nine patients (8 men and 1 woman, mean age 67 ± 4.6 years) with coronary artery disease and exercise-induced chronic stable angina pectoris were studied. Four had old myocardial infarction. No patient had undergone coronary artery bypass surgery. None had clinical or radiographic evidence of congestive heart failure. They did not receive any cardioactive drug for at least 3 days before the study. Each patient signed an informed consent.

The patients underwent 2 bicycle exercise tests, 1 with each formulation of the drug. A 12-lead electrocardiogram was constantly monitored on an oscilloscope and a hard-copy recording was performed every minute throughout the study and during recovery. Exercise was terminated upon development of chest pain similar to that of the anginal episodes that the patients have been having, associated with electrocardiographic ST-segment depression of at least 1 mm. Immediately after termination of exercise the patients received either 1 squirt of ISDN oral spray (Isoket® spray, Schwarz GmbH), equal to 1.25 mg of ISDN, or a sublingual tablet of 5 mg of ISDN. Time to disappearance

of pain was recorded. A similar study was repeated after at least 6 hours, and the patients were crossed over to the other formulation of ISDN.

Results

All patients had chest pain associated with ST-segment depression. Administration of ISDN in both formulations resulted in relief of pain and electrocardiographic changes in all patients. Sublingual ISDN tablets relieved pain within 112.4 ± 67 seconds and oral spray within 61.6 ± 24.4 seconds. The difference was highly significant ($p < 0.0005$). Both formulations were comparably well tolerated. No adverse effects except for mild headaches were observed.

Discussion

We found that ISDN oral spray relieved chest pain twice as rapidly as sublingual tablets (of a higher dose) in elderly patients with chronic stable exercise-induced angina pectoris.

Although sublingual tablet administration is considered the most rapid conventional method for relief of pain in angina pectoris, its effect is not immediate and it has certain limitations. When administered sublingually as tablets, nitrates reach peak plasma levels at least 2 minutes after dissolution of the tablet.[5] However, the time required for dissolution of the tablet varies from patient to patient. Because it takes at least 1 minute, it increases time to peak plasma level by at least 50%.

The time required for the tablet to dissolve depends on various factors and may be prolonged in patients with dry mouth and in those living in a hot climate. Relative dryness of the mouth is more common in elderly than in younger patients, and such patients may require longer periods for dissolution of sublingual tablets.[6] Moreover, elderly distressed patients, mainly those in whom chest pain is associated with dyspnea and tachypnea, find it difficult to hold the tablet under their tongue. In dependent elderly patients the nurse has to follow the patients for several minutes until the tablet dissolves. The use of ISDN oral spray solves all these problems.

Our findings are compatible with those of a pharmacokinetic study, which showed that therapeutic plasma levels of ISDN are achieved several minutes earlier with spray than with sublingual tablets.[7]

The rapidity of action of nitrate oral spray can be clearly demonstrated by hemodynamic evaluation. Kimchi et al[8] reported that hemodynamic effects of nitroglycerin oral spray were evident within 2 minutes in patients with angina pectoris (younger than patients studied by us). We have observed hemodynamic improvement with ISDN spray within 1 minute in patients with pulmonary edema studied with a Swan-Ganz catheter (unpublished data).

The specific oral spray used in this study has a special advantage in the elderly in that it does not require inhalation. Elderly patients may find it difficult to synchronize the administration of spray and rate of breathing.

In summary, ISDN oral spray effectively and rapidly relieves chest pain in patients with angina pectoris. In elderly patients it was shown to act more rapidly than sublingual tablets. It can improve the clinical practice of treatment of angina pectoris.

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Increased Exercise Tolerance and Reduced Duration of Ischemia After Isosorbide Dinitrate Oral Spray in Angina Pectoris

ALAN MARMOR, MD, MICHAEL PLICH, MD, DAVID BLONDHEIM, MD, TALI SHARIR, MD, and JOSEPH S. ALPERT, MD

The prophylactic and therapeutic anti-ischemic efficacy of isosorbide dinitrate (ISDN) oral spray was assessed in 10 patients with coronary artery disease and stable angina pectoris. The patients entered a randomized crossover study of ISDN spray and placebo, involving bicycle exercise testing. Each patient underwent 2 exercise tests at least 4 hours apart. Immediately before initiation of exercise they received either ISDN spray or placebo and crossed over during the other test. ISDN spray delayed the onset of anginal pain by about 40%, from a mean of 5.1 ± 1.4 minutes with placebo to 7.2 ± 1.3 minutes with the active drug ($p < 0.001$). Time of onset of ST-segment depression was also significantly prolonged, from 7.1 ± 1.5 minutes with placebo to 10.2 ± 1.2 minutes with ISDN ($p < 0.001$). The patients achieved a higher double product at onset of pain with ISDN than with placebo. The drug also reduced the time of disappearance of pain after discontinuation of exercise from 3.2 ± 0.7 to 2.1 ± 0.8 minutes ($p < 0.001$), and the time of disappearance of electrocardiographic changes from 4.2 ± 0.6 to 2.5 ± 0.8 minutes ($p < 0.005$). These findings indicate that oral ISDN spray is an effective prophylactic for exercise-induced angina. Its rapid onset of action makes it especially suitable for usage immediately before exercise.

(Am J Cardiol 1988;61:4E–6E)

Isosorbide dinitrate (ISDN) is widely used for the treatment (sublingual tablets) and prevention (oral tablets and transdermal delivery systems) of attacks of angina pectoris. Even the most rapid method of administration, sublingual tablets, takes at least 2 minutes until the onset of effect. Usually this takes some more time because 2 minutes are the required time for nitrates administered in sublingual tablet form to reach peak plasma levels.[1] However, an additional period is required for dissolution of the tablet, which has to take place, at least partially, before absorption begins. This period shows interpatient variability and further delays onset of action.

It is a common practice to administer nitrates in the form of sublingual tablets before effort that is known to cause chest pain in patients with angina pectoris. Because of the reasons discussed, the onset of this effect takes several minutes. Although this is usually sufficient for most patients with angina pectoris, a more rapid method of administration is desirable.

We assessed the antianginal efficacy of ISDN spray (Isoket® spray, Schwartz GmbH) in patients with exercise-induced angina pectoris in order to determine and quantitate its time course.

Methods

Patients: Ten patients (6 men and 4 women), aged 49 to 68 years (mean 58.9 ± 6.2) were included in the study. All patients had chronic stable angina pectoris with positive exercise test results (exercise-induced angina associated with ischemic ST-segment depression of 1.5 mm or more, lasting at least 0.08 second) and angiographically proved coronary artery disease. Five patients have had a myocardial infarction at least 4 months before the study. No patient had undergone coronary artery bypass surgery. No patient had evidence of congestive heart failure or systemic or pulmonary hypertension. Before the study, all patients were

From the Rebeca Ziev Medical Center, Safad, Israel and the University of Massachusetts Medical School, Boston, Massachusetts.

Address for reprints: Alan Marmor, MD, Department of Cardiology, Rebeca Ziev Medical Center, Safad, Israel.

known to tolerate sublingual nitroglycerin or ISDN, or both.

Isosorbide dinitrate oral spray: The ISDN spray is a watery solution enclosed in a metal aerosol container and provides 1.25 mg ISDN in each squirt of Isoket. Inhalation of the drug is not required and it is administered on the lingual and other oral mucosa.

Protocol: In the morning of the study all patients underwent physical examination and electrocardiography at rest. The patients were then prepared for exercise testing. Immediately before the initiation of exercise, they received in a randomized single-blind order, either 1 squirt of placebo or of ISDN sprayed on the tongue. Exercise testing was performed according to a 3-minute-stage protocol, starting with 25 W and increasing the load by this extent every 3 minutes. The endpoint of the study was chest pain, similar to that experienced by the patient during effort. The patients were instructed to inform the investigator immediately of onset of chest pain, of chest pain comparable to that experienced during effort before the study and of the time at which chest pain completely subsided after termination of exercise.

All cardioactive drugs were withdrawn before the study. Beta blockers were discontinued 7 days before the study and calcium antagonists 2 days before. In these last 2 days only sublingual nitrates were used, if required. During exercise and recovery a 12-lead electrocardiogram was recorded every 30 seconds and electrocardiographic leads 1, aVF and V_5 were constantly monitored. Heart rate and blood pressure were recorded in the sitting position before, every minute during and at termination of exercise, and during the recovery period. Time to onset of angina and to appearance of 1.0 mm of ST-segment depression lasting at least 0.08 second, and time of disappearance of pain and of ST-segment depression after discontinuation of exercise were measured. The paired *t* test was used for statistical analysis.

Results

Effect on ischemia: ISDN spray delayed the onset of angina and electrocardiographic ischemic changes in all patients. Exercise time to pain was 5.1 ± 1.4 minutes with placebo and 7.2 ± 1.3 minutes with ISDN ($p < 0.001$). Time to appearance of ST-segment depression was 7.1 ± 1.5 minutes with placebo and 10.2 ± 1.2 minutes with ISDN. Time of disappearance of pain after discontinuation of exercise was shortened from 3.2 ± 0.8 minutes with placebo to 2.1 ± 0.8 minutes with ISDN ($p < 0.001$). Time to disappearance of ST-segment depression was shortened from 4.2 ± 0.6 to 2.5 ± 0.8 minutes, respectively ($p < 0.005$).

Hemodynamic effects: Heart rate and systolic and diastolic blood pressure before exercise were not significantly different before the trial with placebo and with ISDN. At termination of exercise, systolic blood pressure increased from 163.5 ± 17.3 mm Hg with placebo to 192.5 ± 15.7 mm Hg with ISDN ($p < 0.001$). Diastolic blood pressure was not significantly different. Heart rate was 129.5 ± 16.8 beats/min with placebo and 142.5 ± 11.2 with ISDN ($p < 0.001$). Double product increased from 21,370 ± 4,613 to 27,535 ± 32,800 ($p < 0.001$).

Adverse effects: Two patients had transient headaches and 1 patient had transient dizziness with a slight decrease in blood pressure after ISDN. All patients completed the study without having major adverse effects.

Discussion

Our previous experience with ISDN spray suggests that because of its rapid action, it may be superior to sublingual nitrate tablets. Previously, we observed that ISDN spray exerts a beneficial hemodynamic effect within less than 30 seconds in patients with acute pulmonary edema and that the spray relieves exercise-induced chest pain and electrocardiographic changes 30 to 50% more rapidly than sublingual tablets of ISDN. The onset of effect is more rapid with ISDN spray than with intravenous infusion. This is not only because of the time required to start an intravenous line but also because of first-pass metabolism of nitrates in the liver, which is avoided when oral spray is used.[2,3] Therefore, this formulation was chosen for evaluation as pre-effort therapy in patients with exercise-induced angina pectoris. Because of the rapid onset of action, the spray is especially suitable for use immediately before initiation of exercise and the patient does not have to wait until dissolution of a tablet.

The present study revealed that ISDN spray, administered immediately before the initiation of exercise, increased exercise tolerance in patients with chronic stable angina pectoris. The drug increased exercise duration by about 40%. This finding is comparable to results achieved with sublingual nitroglycerin tablets[4–7] and nitroglycerin oral spray.[8] This increase was associated with the usual cardiocirculatory effects of nitrates. ISDN also did not significantly lower diastolic blood pressure. When considerable autoregulatory coronary dilation has been achieved, as may be expected in patients with coronary artery disease who exercised to myocardial ischemia, myocardial flow distal to a fixed coronary stenosis has been shown to be directly related to perfusion pressure.[9,10] In the presence of peripheral vasodilation accompanying exercise, a vasodilator that excessively lowers diastolic blood pressure may impair coronary perfusion. As ISDN reduces left ventricular filling pressure, myocardial flow may increase in relation to a given perfusion pressure.

ISDN also significantly shortened the duration of chest pain and ST-segment depression. The effect of ISDN spray given as a prophylaxis immediately before exercise is equivalent to the effects achieved by nitrates administered at the onset of pain.

Kimchi et al[8] showed that nitroglycerin oral spray is an effective prophylactic for exercise-induced angina pectoris. The drug delayed or abolished the appearance of chest pain and ST-segment depression. The patients achieved a higher heart rate at peak exercise with nitroglycerin spray, associated with a decline in

the maximal exercise-induced ST-segment depression. Our results with ISDN are in accordance with those effects of nitroglycerin. However, ISDN has a longer half-life than nitroglycerin.[11,12] Therefore, it should be theoretically superior in its duration of action. ISDN spray, which combines both very rapid onset of action and relatively prolonged efficacy, has advantages as a prophylactic before exercise in patients with chronic stable angina pectoris. Another difference between the studies is that Kimchi et al[8] gave the drug 2 minutes before initiation of exercise. This early administration is required for sublingual tablets but, in our opinion, not necessary for the spray. The rapidity of action of the spray allows administration immediately at the initiation of exercise, as we did in this study. The spray has another theoretical advantage over tablets: The active drug is protected in the container while the tablets are repeatedly exposed when the bottle is opened. This may result in chemical degradation of the tablets.

In summary, ISDN spray is an effective prophylactic agent for use before initiation of exercise in patients with chronic stable angina pectoris. It not only increases the duration of exercise and delays the onset of pain and ischemic electrocardiographic changes but also shortens the duration of the ischemia when it does develop.

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Nitroglycerin Oral Spray: Evaluation of Its Coronary Artery Dilative Action by Quantitative Angiography

KURT F. BACHMANN, MD, and ROLF E. GANSSER, MD

Twenty patients were studied angiographically before and after administration of glyceryl trinitrate (NTG) spray at a single oral dose of 0.8 mg in either a hydrosoluble (NTG-h) or liposoluble (NTG-l) solution. The assessment was by a randomized double-blind trial involving quantitative coronary angiography and pharmacologic stress testing using ergonovine maleate. The peak effect and duration of NTG-induced coronary dilatation were evaluated in 2 groups of 10 patients each, in whom NTG oral spray was given either under resting conditions (group A) or for the release of ergonovine-increased coronary vasomotor tone (group B). The study demonstrates that the 2 different galenic formulations of NTG spray are equally efficacious in dilating the conductance coronary arteries under both conditions.

When NTG-h and NTG-l oral spray were given subsequent to ergonovine-testing, the diameters of extramural coronary arteries are not only reset to their dimensions at baseline but furthermore increase above resting values by 15.1% and 15.5%, respectively. Ergonovine-induced coronary vasoconstriction was released significantly for a period of at least 30 minutes. Both the NTG-h and NTG-l oral spray are potent coronary vasodilators in patients with increased coronary vasomotor tone.

(Am J Cardiol 1988;61:7E–11E)

The downfall of organic nitrates in the long-term therapy of stable angina pectoris in the early 1970s[1] was followed by a decade of its recovery due to the development of long-acting nitrates such as isosorbide dinitrate and its metabolite isosorbide-5-mononitrate. Nevertheless, glyceryl trinitrate (NTG) has remained the "emergency nitrate" for the relief not only of anginal attacks but also for hemodynamic unloading in acute congestive heart failure, acute pulmonary hypertension and valvular insufficiency.

Hemodynamic unloading with a reduction of preload and afterload is considered to be the main beneficial effect of NTG in the relief of myocardial ischemia and in the improvement of depressed left ventricular performance.[2] Furthermore dilatation of coronary stenoses has been documented as a major component of the drug response.[3]

NTG is currently available in different galenic formulations for sublingual (tablet and capsule), transdermal (patch and ointment), parenteral and even rectal (rectal uvula) application. NTG aerosol spray for oral use has been available in West Germany for several years and has been studied with regard to improvement in exercise tolerance[4] and hemodynamic responses.[5–7] However, up to the present, the acute coronary dilative effect of NTG has been evaluated by quantitative coronary angiography in patients under resting conditions only.[3,8–10]

We evaluated the coronary dilative properties of a new hydrosoluble NTG lingual spray in patients with stable, exercise-induced angina pectoris and in patients with atypical chest pain during diagnostic ergonovine-provocation.

Methods

Nitroglycerin spray: A spray aerosol contains holds 10 ml of NTG solution and delivers about 2 doses at 0.4 mg at each spray. The standard spray contains NTG in aromatized liposoluble formulation (NTG-l), and the test spray in hydrosoluble formulation (NTG-h). In this study, spray containers looking identical in shape, size and color were used holding either NTG-l or NTG-h.

Patients: Two groups of 10 patients each were studied. Group A included 10 patients (9 men and 1 woman, ranging in age from 39 to 77 years [mean 56]) with stable exertional angina pectoris, a positive result on exercise testing and a more than 75% diameter stenosis in at least 1 major coronary artery.

From the Med. Klinik II und Poliklinik (Cardiology) University of Erlangen-Nuernberg, Federal Republic of Germany.

Address for reprints: Prof. Dr. med. K. Bachmann, Med. Klinik II und Poliklinik (Cardiology), Universitaet Erlangen-Nuernberg, Oestl. Stadtmauerstr. 29, D-8520 Erlangen, Federal Republic of Germany.

Group B consisted of 10 patients (5 men and 5 women, ranging in age from 54 to 66 years [mean 60]). All patients had a nonexertional, atypical form of chest pain and a negative exercise stress test result. Coronary angiograms demonstrated in 3 of these patients a coronary diameter narrowing between 51% and 75% in at least 1 major coronary artery. Two patients had a stenosis of less than 50% diameter reduction in 1 major coronary artery, 4 patients had angiographically normal coronary arteries, and 1 patient had a myocardial bridging of the left anterior descending coronary artery.

Informed consent was obtained from all patients before the invasive investigations. Long-acting nitrates, β-blocking drugs and calcium antagonists were discontinued 24 hours before the study.

Study protocol: The investigation consisted of a double-blind trial during which patients received either NTG-h or NTG-l oral spray in random fashion. Keeping the container vertical, NTG spray was administered orally at a total dose of 0.8 mg within 2 seconds, delivered per 2 metered doses of 0.4 mg each. A Sones catheter was placed across the brachial artery into the aortic root; after a 30-minute period of rest, baseline coronary angiograms were recorded. In group A, NTG spray was given after baseline coronary angiography and in group B, after angiographic controls following ergonovine provocation. Ergonovine testing was performed by sequential intravenous bolus injections of 0.1, 0.2 and 0.4 mg ergonovine maleate at 5-minute intervals. Three minutes after the last ergonovine bolus injection, coronary angiograms were recorded again to assess coronary vasoconstriction. Throughout this study, continuous electrocardiographic monitoring was performed and blood pressure in the pulmonary artery and the aorta was maintained.

Quantitative coronary angiography: Coronary angiography was repeated at intervals of 6, 15 and 30 minutes after the administration of NTG spray. Care was taken that within an individual patient the rotation of skew angles, height and magnification factors of the image intensifier were not altered during the study. Coronary angiograms with a spatial resolution of 4.5 LP/mm were obtained by using a high-resolution 7-inch image intensifier, a 35-mm cine technique with 25 frames/s and Omnipaque 300® (Schering) as contrast material. Frames filmed in end-diastole were selected for quantitative analyses at each condition.

Quantitative coronary analyses were performed with the computer-based Coronary-Angiography-Analysis-System.[11] The systems variability of repeated analyses in absolute dimension is less than 0.1 mm.[11] Coronary diameters were measured using automated contour detection and correction of pincushion distortion. The tip of the Sones catheter was placed into the ostium of a coronary artery and used as a scaling device for conversion of units in millimeters. In each individual patient coronary diameters were measured in angiographically normal, proximal segments of the left anterior descending, left circumflex and right coronary arteries. Thus, results are based on the measurements of 30 coronary segments in group A and in group

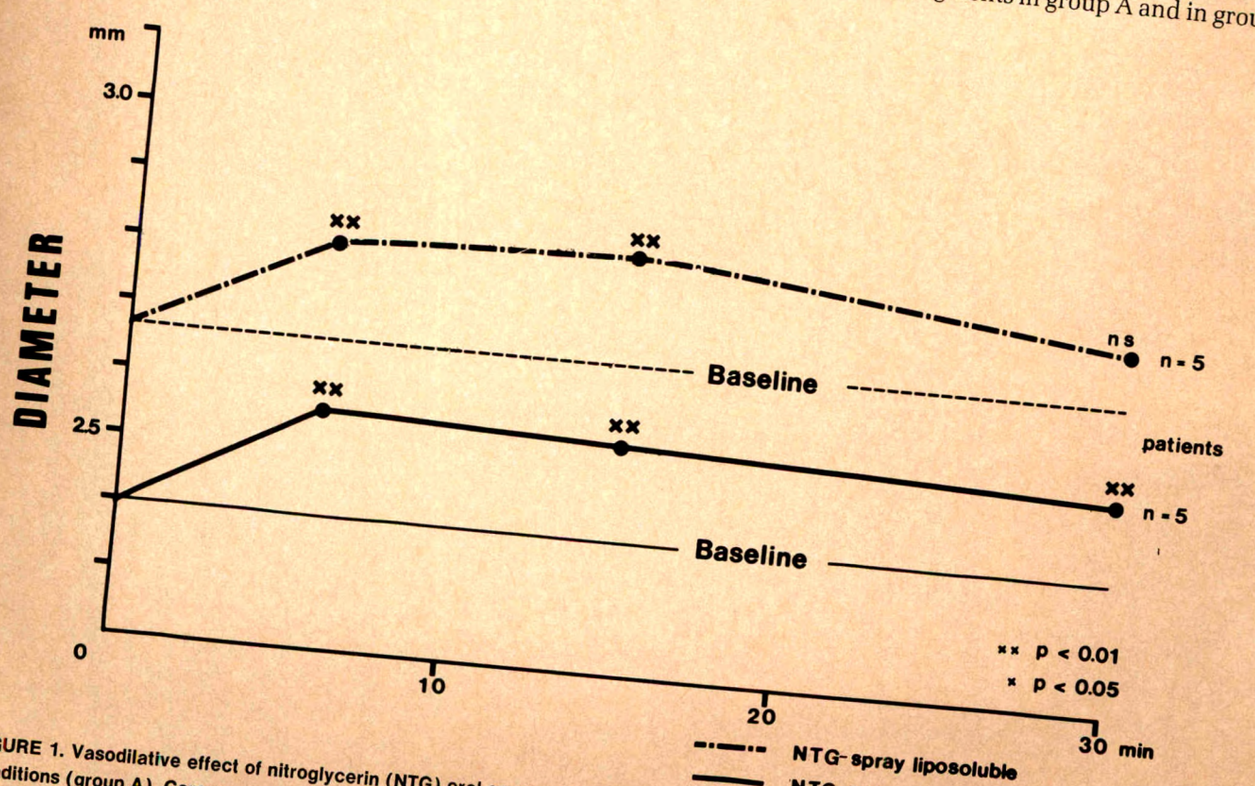

FIGURE 1. Vasodilative effect of nitroglycerin (NTG) oral spray on the diameter of coronary conductive vessels in patterns under resting conditions (group A). Coronary diameters are expressed as mean ± standard deviation out of 15 coronary segments for each NTG spray. ns = not significant.

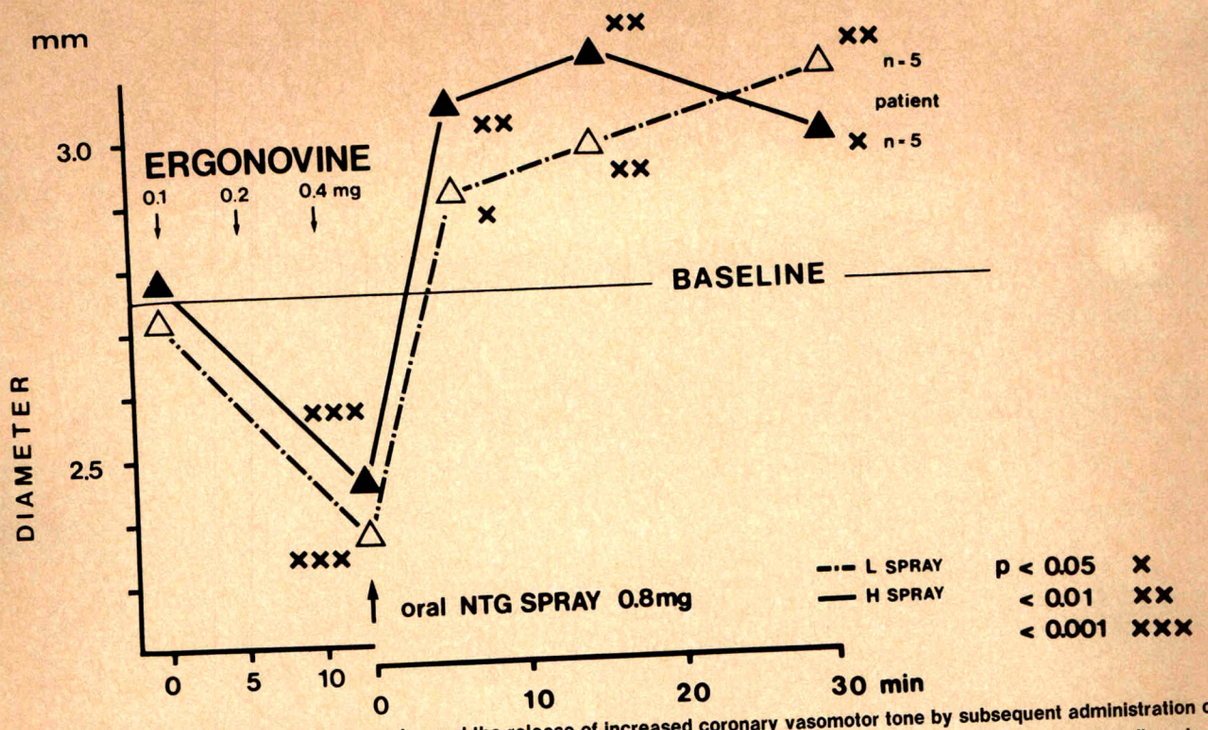

FIGURE 2. Vasoconstrictive effect of ergonovine and the release of increased coronary vasomotor tone by subsequent administration of nitroglycerin (NTG) oral spray. NTG is efficacious in releasing ergonovine-induced vasoconstriction with increasing coronary diameters above baseline values. H = hydrosoluble; L = liposoluble.

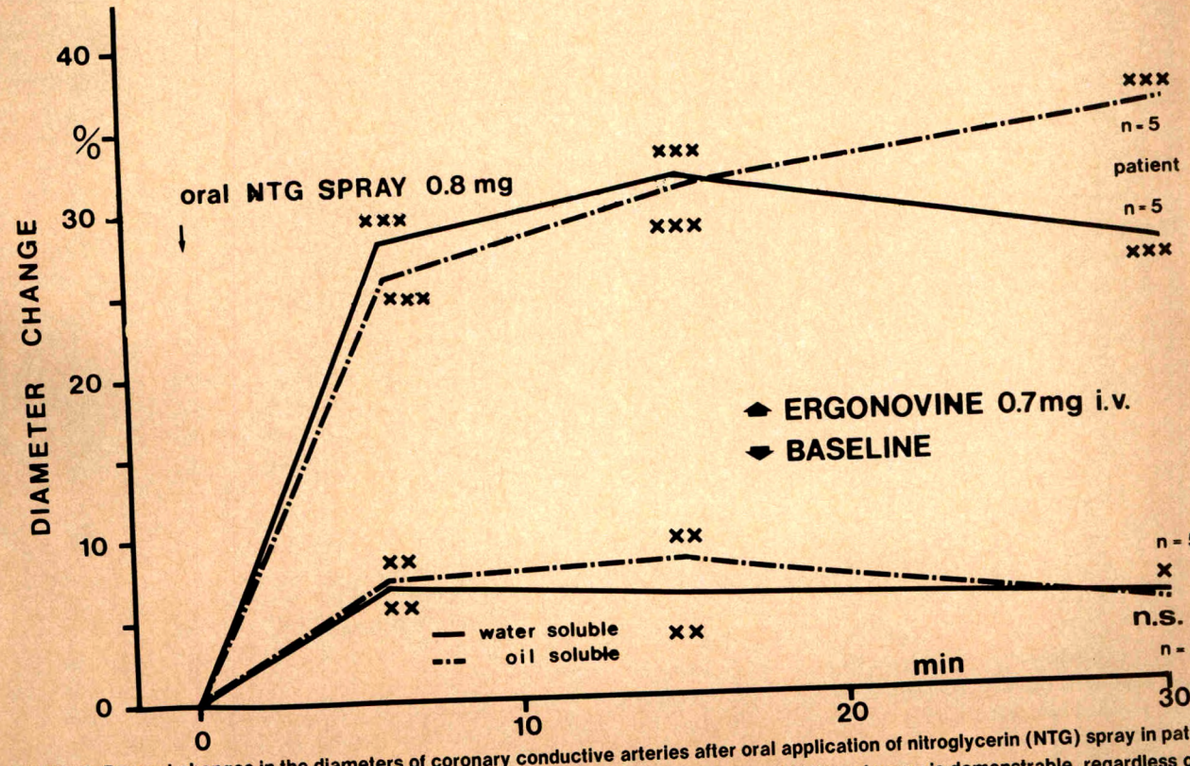

FIGURE 3. Percent changes in the diameters of coronary conductive arteries after oral application of nitroglycerin (NTG) spray in patients under resting conditions and during ergonovine provocation. Coronary dilative action of NTG oral spray is demonstrable, regardless of the galenic formulation, during a period of at least 30 minutes in group B patients undergoing ergonovine provocation. i.v. = intravenous; n.s. = not significant.

B. Coronary diameters at 6-, 15- and 30-minute intervals after administration of NTG oral spray were compared to diameters at rest in group A and to diameters at rest and after ergonovine provocation in group B. Changes in coronary diameters were calculated in millimeters and percent change.

Statistical methods: The significance of changes in coronary diameters within an individual patient was assessed by a Wilcoxon matched-pairs test. Significance of differences between NTG-h and NTG-l was determined by a Mann-Whitney U Test with regard to the extent and duration of action. Values at $p < 0.05$ were considered significant.

Results

Effect of nitroglycerin spray on coronary diameters at baseline: NTG oral spray induced a significant coronary vasodilation in group A patients: NTG-h increased coronary diameters from 2.40 ± 0.48 to 2.56 ± 0.51 mm ($p < 0.01$), 2.54 ± 0.55 mm ($p < 0.01$) and 2.53 ± 0.54 mm ($p < 0.01$) after 6, 15 and 30 minutes (Fig. 1). NTG-l increased coronary diameters from 2.64 ± 0.50 to 28.1 ± 0.44 mm ($p < 0.01$), 2.83 ± 0.43 mm ($p < 0.01$) and 2.74 ± 0.46 mm, respectively (difference not significant) (Fig. 1). There was a percent change in coronary diameters of 6.9, 6.0 and 5.2% after administration of NTG-h and a change of 7.4, 8.2 and 4.7% after administration of NTG-l (Fig. 3).

There was no significant difference between NTG-h and NTG-l in the extent and duration of vasodilative action in this group of patients.

Effect of ergonovine on coronary diameters at baseline: Intravenous ergonovine at a total dose of 0.7 mg decreased coronary diameters from 2.76 ± 0.72 to 2.45 ± 0.71 mm ($p < 0.001$) in group B patients who subsequently received NTG-h, and from 2.71 ± 0.62 to 2.37 ± 0.65 mm ($p < 0.01$) in group B patients who received NTG-l (Fig. 2). Compared with baseline values, this was a reduction in coronary diameters of 11.5 and 13.5%, respectively.

Effect of nitroglycerin spray on coronary vasoconstriction after ergonovine: NTG oral spray was efficacious in releasing ergonovine-induced coronary vasoconstriction in the group B patients: NTG-h spray increased coronary diameters after ergonovine from 2.45 ± 0.71 to 3.05 ± 0.60 mm ($p < 0.001$), 3.12 ± 0.62 mm ($p < 0.001$) and 3.00 ± 0.61 mm ($p < 0.001$), 3.12 ± 0.62 mm ($p < 0.001$) and 3.00 ± 0.61 mm ($p < 0.001$) at 6-, 15- and 30-minute intervals (Fig. 2 and 4). This was a 28.1, 31.5 and 27.0% diameter increase compared with diameters after ergonovine (Fig. 3), which exceeded baseline values by 12.4% ($p < 0.01$), 15.1% ($p < 0.01$) and 10.7% ($p < 0.05$), respectively. Coronary diameters after NTG-l measured 2.91 ± 0.63 mm ($p < 0.001$), 2.98 ± 0.53 mm ($p < 0.001$) and 3.10 ± 0.65 mm ($p < 0.01$), compared with 2.37 ± 0.65 mm after ergonovine (Fig. 2). There was a diameter increase of 25.6, 30.7 and 35.5% in relation to diameter narrowing after ergonovine (Fig. 2), and a diameter increase of 7.8% ($p < 0.05$), 11.6% ($p < 0.05$) and 15.5% ($p < 0.01$) compared with baseline values, respectively.

Whereas all changes of coronary diameters during ergonovine provocation and subsequent NTG application were statistically highly significant, no differences were seen when NTG-h and NTG-l oral spray in extent and duration of action were compared.

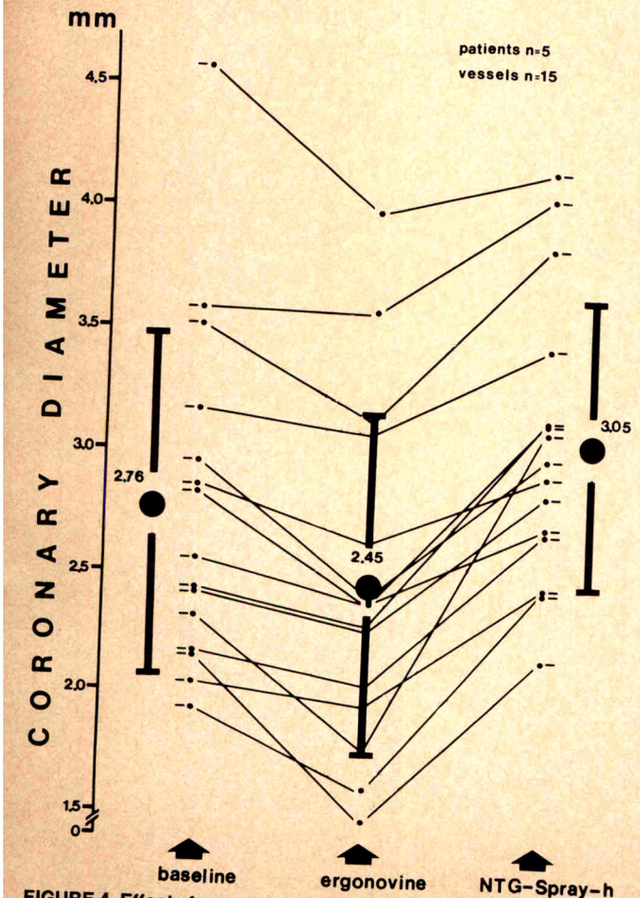

FIGURE 4. Effect of ergonovine and subsequent NTG-h oral spray on 15 coronary segments in the 5 group B patients who were randomized to NTG-h. Vasoconstriction after ergonovine and vasodilation after NTG was found to occur in a regular way in all of the coronary segments. NTG spray induces a marked coronary artery dilatation that exceeds dimensions at baseline. h = hydrosoluble.

Discussion

This study demonstrates for the first time the coronary artery dilating properties of NTG oral spray in patients with ergonovine-induced coronary vasoconstriction and the effectiveness of a new, hydrosoluble formulation of NTG oral spray. This new NTG spray, given orally at a dose of 0.8 mg, resulted in equal coronary vasodilative action compared with NTG oral spray in oily solution, which served as a standard in this study. Quantitative angiography demonstrated coronary vasodilation after NTG oral spray not only in patients under resting conditions but also in patients undergoing ergonovine-provocation. When NTG oral spray was given in addition to ergonovine, it counteracted not only the pharmacologically induced coronary vasoconstriction, but also increased coronary arteries above baseline diameters.

Hemodynamic investigations had priority to quantitative coronary angiography in this study, and there-

fore the onset of vasodilative action could not be assessed because of the 6-minute delay of the first angiographic control after NTG administration. But nevertheless, a marked coronary dilative action was demonstrable 6 minutes after administration of NTG spray and the duration of action was seen during a period of 30 minutes.

Further studies are needed to evaluate the onset of coronary dilative action of NTG spray by control angiograms within the first minute after its application.

The antianginal effect of NTG is mainly related to the reduction of preload and afterload with a concomitant decrease in both diastolic and systolic ventricular wall tension.[2] In addition to its reduction in myocardial oxygen demand, NTG has a coronary vasodilative action that improves myocardial oxygen supply, and this may contribute substantially to both the improvement of myocardial perfusion and myocardial performance.

NTG oral spray provides a method of achieving the beneficial effects of NTG in a more convenient way for the patient. It is evident from our hemodynamic studies that the new, hydrosoluble formulation of NTG oral spray has a more rapid onset of action compared with the conventional liposoluble NTG spray.

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Sustained-Release Isosorbide Mononitrate (50 mg): Optimization of a Once-Daily Dosage Form for Long-Term Treatment of Angina Pectoris

RAINER BONN, PhD

A capsule formulation containing 50 mg of isosorbide mononitrate has been developed, 30% of which is in a nonsustained-release form to ensure rapid attainment of initial nitrate plasma levels. The remaining 70% is in a sustained-release form that ensures a long-lasting effect and the convenience of once-daily dosing. This formulation of sustained-release isosorbide mononitrate (Elantan® LA 50 mg) provides plasma levels greater than 100 ng/ml for 17 hours after oral administration. For the remaining 7 hours, the nitrate plasma level ranges between 50 and 100 ng/ml. (Am J Cardiol 1988;61:12E–14E)

The introduction of isosorbide 5-nitrate (isosorbide mononitrate [ISMN]) in the therapy of angina pectoris has facilitated long-term treatment. ISMN has a half-life of 4 to 5 hours and therefore has longer lasting effects than other nitrates. Nevertheless, this drug must be administered 2 to 3 times daily in the form of tablets, which releases the drug rapidly. From the viewpoint of a dosage schedule convenient to the patient, patient compliance and therapeutic reliability, there was a need to develop an ISMN preparation whose drug release is controlled (a sustained-release formulation) and allows once-daily administration.

Methods

The study was carried out in the form of a randomized crossover trial involving 18 male healthy volunteers, aged between 18 and 41 years (mean 25.5). Each subject received either 20 mg of ISMN (Elantan® tablets) twice daily or 50 mg of slow-release ISMN (Elantan LA 50) once daily over 5 days in a randomized crossover design. The tests were performed under conditions meeting GLP requirements by Simbec Research.[1] On the fifth day of the experiment, plasma concentrations were determined over the entire dosage interval, by high-performance liquid chromatography, using the procedure of Maddock et al.[2] No subject was subsequently excluded from the study.

From the Department of Clinical Pharmacology, Schwarz GmbH, D-4019 Monheim, Federal Republic of Germany.

Address for reprints: Rainer Bonn, Department of Clinical Pharmacology, Schwarz GmbH, D-4019 Monheim, Federal Republic of Germany.

Results

Plasma levels: Figure 1 shows the mean ISMN plasma concentration time curve after 50 mg of sustained-release ISMN (Elantan LA) had been taken once daily for 4 days. In the steady state, immediately before administration in the morning, the minimal plasma concentration of ISMN, c^{ss}_{min} was 40 to 50 ng/ml. After the conventional tablet (20 mg of ISMN twice daily every 12 hours), the corresponding value was 80 to 90 ng/ml. After administration of Elantan LA, the plasma concentration increased rapidly and reached a value of 300 ng/ml after 1 hour. The increase in concentration was then reduced, and after 6 hours a mean maximal concentration (c^{ss}_{max}) of 490 ng/ ml was reached. The concentration then slowly declined. Plasma ISMN levels of over 100 ng/ml were maintained for 17 hours, compared with 10 hours after conventional tablets.

The pharmacokinetic parameters relating to ISMN after the 2 preparations, obtained by averaging the individual values, are shown in Table I.

Retardation: According to Meier et al,[3] retardation of the release of an active drug compared with the normal dosage form can be characterized by the 2 retard quotients R_Δ (ratio of half-value duration) and R_c (ratio of c_{max} values). In this study, the half-value duration was prolonged by a factor of 2.4 ± 0.8, without significant elevation of the maximal plasma concentrations ($R_c = 1.2 \pm 0.4$).

Mean residence time of ISMN within the body was prolonged from 7.2 hours (Elantan tablets) to 9.8 hours (Elantan LA 50). The mean in vivo dissolution time of

the sustained-release preparation was therefore 2.6 hours. Relative bioavailability of Elantan LA 50 was 84% of Elantan tablets (differences were not statistically significant).

No adverse reactions were reported.

Discussion

Previous studies: Jansen et al[4] found a blunting effect (i.e., tolerance development) with regard to pulmonary artery pressure and working capacity when ISMN, 50 mg, was given 3 times daily at 8-hour intervals over a period of 4 weeks. When ISMN was reduced to 20 mg administered 3 times daily, no development of tolerance was observed.[5]

A pharmacokinetic analysis of ISMN plasma concentrations based on measured and calculated values according to the dosage regimen from Jansen allows the following interpretation (Fig. 2): After 50 mg of ISMN was administered 3 times daily at 8-hour intervals, steady-state maximal plasma concentrations of more than 1,000 ng/ml and minimal plasma concentrations of approximately 500 ng/ml were obtained. After 20 mg of ISMN was administered 3 times daily, maximal plasma concentrations of less than 500 ng/ml and minimal levels of 150 ng/ml were achieved. After 20 mg of ISMN was given twice daily, the minimal levels decreased below 100 ng/ml.

It was concluded from these investigations that levels of ISMN above 500 ng/ml should be avoided, as should fluctuations between 500 and 1,000 ng/ml. Plasma concentrations of ISMN should range between 100 and 500 ng/ml during active phases of the day, but may decrease below 100 ng/ml during the "trough" or inactive phase.

Cowan[6] also suggests that "prophylaxis should be tailored to the individual to provide protection at times of maximum susceptibility to ischemia, while allowing nitrate levels to fall at other times," i.e., during the night.

Working hypothesis for the present study: One way of increasing the duration of action of ISMN, and thereby reducing the dosage frequency and improving

TABLE I Parameters Relating to the Assessment of Bioavailability and Retardation of Release from Sustained-Release Isosorbide Mononitrate (ISMN) (Elantan® LA)

Parameter	ISMN (20 mg Twice Daily)	ISMN Sustained-Release (50 mg Once Daily)
c^{ss}_{min} (0)(ng/ml)	87 ± 47	38 ± 21
c^{ss}_{min} (τ)(ng/ml)	76 ± 47	44 ± 40
c^{ss}_{max}(ng/ml)	436 ± 138	488 ± 129
AUC^{ss}(ng h/ml)	2,377 ± 751	5,029 ± 1,272
MRT(h)	7.2 ± 0.8	9.8 ± 0.9

Values are expressed as mean ± standard deviation.

AUC = area under the curve; R_c = 1.21 ± 0.44; R_Δ = 2.35 ± 0.83; Relative bioavailability = 83.9 ± 6.7; c^{ss}_{min} = steady-state minimal plasma concentration; c^{ss}_{max} = steady-state maximal plasma concentration.

Retard quotients: R_c = ratio of c_{max} values; R_Δ = ratio of half-value duration; MRT = mean residence time.

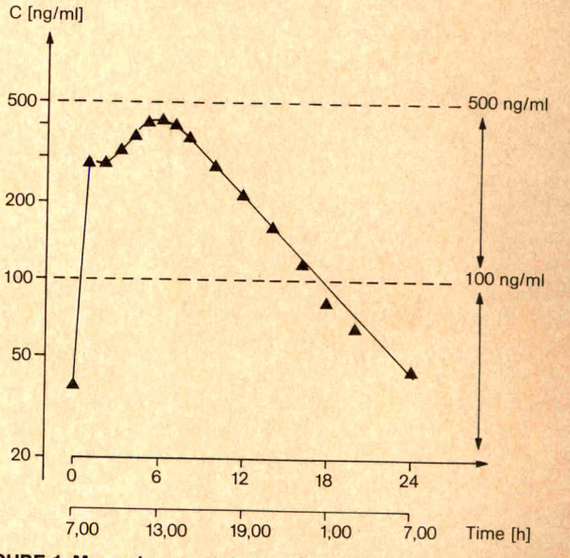

FIGURE 1. Mean plasma concentration of isosorbide mononitrate in 18 healthy volunteers after administration of 50 mg of sustained-release Elantan® LA 50 for 4 days. Semilogarithmic scale.

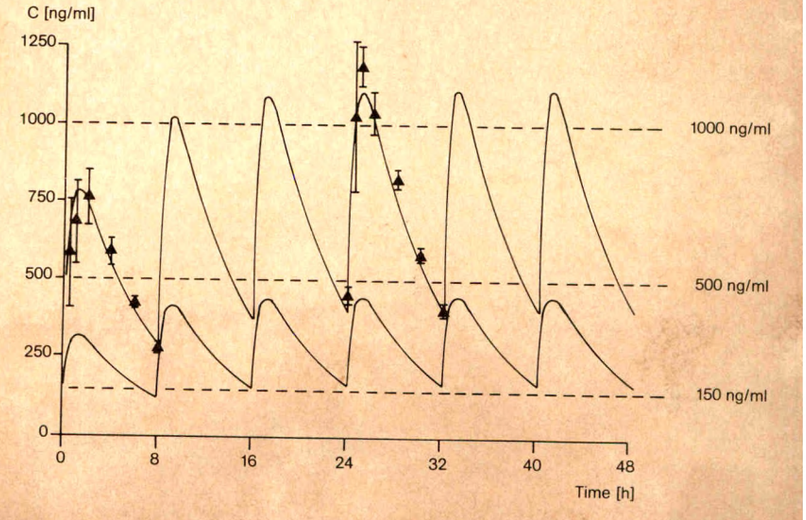

FIGURE 2. Measured (▲) and calculated (—) plasma concentrations of isosorbide mononitrate after oral administration of 20 mg 3 times daily (*lower curve*) and 50 mg 3 times daily (*upper curve*). The dosage interval was 8 hours in all cases. Steady-state concentrations were reached after the fourth dose.

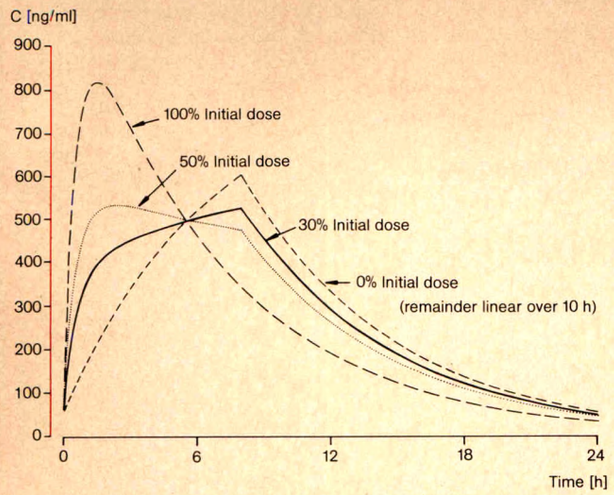

FIGURE 3. Calculated isosorbide mononitrate plasma concentration curves after oral administration of 50 mg in sustained-release form and in nonsustained-release form.

patient compliance, is to coat the active drug with a sustained-release capsule. To achieve optimal plasma levels, the design of the sustained-release matrix is extremely important.

If all of the nitrate is released continuously in vivo over a period of 8 hours (i.e., if there is no initial release dose), a slow increase in plasma nitrate concentrations would be expected, with a maximal concentration after 8 hours. The minimal therapeutic level of 100 ng/ml would be reached relatively late, leaving the patient unprotected.

This "lag-period" can be reduced by an initial nonsustained-release dose. If this is 35% of the total nitrate content and the sustained-release dose would be absorbed linearly over 8 hours, persistently high or plateau plasma concentrations would be expected over a lengthy period (Fig. 3).

If this initial dose is greater than 35%, the maximal concentration would be reached shortly after administration, decreasing slowly. If the initial dose is less than 35%, the maximal plasma nitrate concentration would be reached after 8 hours. Therefore, an initial dose of 30% of the total was used (Fig. 3), which led to an increase in nitrate plasma levels for 6 hours, followed by a slow decline. This ratio is in accordance with the current opinion regarding the prevention of nitrate tolerance.[5–10]

Conclusions

This preparation of sustained-release ISMN, 50 mg (Elantan LA 50), reached a plasma concentration of 300 ng/ml after 1 hour. The nitrate plasma level remained above 100 ng/ml for 17 hours after administration. During the remaining 7 hours, plasma nitrate levels ranged between 50 and 100 ng/ml, which may offer protection against silent (i.e., asymptomatic) myocardial ischemia and slight physical stress. Clinical studies with this 50-mg formulation have demonstrated significant antianginal efficacy when compared with placebo therapy after acute[11] and subacute[12] dosages, and no tolerance development after 3 and even 12 months of therapy.[13–15] This 50-mg nitrate formulation is suitable for once-daily dosage.

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Nitrates and Calcium Antagonists for Silent Myocardial Ischemia

THOMAS VON ARNIM, MD, and ANDREA ERATH, MD

Continuous Holter monitoring of patients with coronary heart disease can show transient ischemic episodes occurring spontaneously with or without angina throughout the day. A controlled double-blind trial was conducted comparing the effects of isosorbide-5-mononitrate (IS-5-MN) and nifedipine in patients with documented transient ischemic episodes. Seventy-five percent of the ischemic episodes were not accompanied by pain. Twenty patients with documented coronary heart disease were included; 15 finished the 4-week study (1 patient had headaches, 1 thyrotoxicosis, 1 hypertensive crisis and 2 unstable angina). On a dual-channel FM-recorded electrocardiogram, ischemic episodes were counted when ST deviation was >1 mm for >1 minute. Patients received IS-5-MN (20 mg 3 times a day or 50 mg in a sustained-release tablet) or nifedipine (20 mg in a sustained-release tablet 3 times a day) in random order over four 1-week periods. At the end of each week, Holter monitoring was repeated and showed reductions of episodes by 67% and 67% after weeks of IS-5-MN therapy and 56% and 58% after weeks of nifedipine therapy (all p <0.05). Painful and painless episodes were reduced to a similar extent. Individual responses showed great variability, and in all treatment periods not more than half of the patients were completely free of ischemic episodes. One of the 12 patients did not respond to either way of treatment. It is concluded that (1) treatment effects for transient, predominantly silent, ischemia can be documented with continuous Holter monitoring; (2) both IS-5-MN and nifedipine reduce ischemic episodes by about 60%; and (3) large variability and incomplete response in some patients may make combination treatment a reasonable choice.

(Am J Cardiol 1988;61:15E–18E)

Several investigators[1–4] have shown that transient ischemia with or without angina pectoris can be objectively documented by ambulatory electrocardiographic (ECG) monitoring. With use of careful nuclear medical studies,[5] transient ST changes have been validated to represent true ischemia in patients with severe underlying coronary disease.

If ambulatory monitoring can objectively document ischemia in patients throughout the day, then it would appear reasonable to use this technique for the objective assessment of treatment effects. We therefore conducted a double-blind trial, comparing the influence of 2 well-known antianginal drugs, isosorbide-5-mononitrate (IS-5-MN) and nifedipine, on episodes of transient ischemia in patients with documented coronary heart disease.

From the Klinikum Grosshadern, Medizinische Klinik I, Marchioninistr. 15, 8000 München 70, Federal Republic of Germany.

Address for reprints: Priv. Doz. Dr. Th. v. Arnim, Klinikum Grosshadern, Medizinische Klinik I, Marchioninistr. 15, 8000 München 70, Federal Republic of Germany .

Method

Patients: The study included consecutive outpatients of our department, who had coronary heart disease documented either by coronary angiography or by definite myocardial infarction from history and ECG criteria, and who had more than 1 transient ischemic episode on ambulatory monitoring when they were not taking long-acting nitrates or calcium antagonists.

We included 20 such patients (14 men and 6 women, median age 64 years). All patients gave informed consent. During the study 5 patients had to be withdrawn for the following reasons: severe headaches (n = 1), development of thyrotoxicosis (n = 1), hypertensive crisis (n = 1) and unstable angina (n = 2). The following results are based on evaluation of the remaining 15 patients.

Ambulatory electrocardiographic monitoring: The method of ambulatory monitoring with analysis of ST-segment changes has been described elsewhere.[6] A typical example of an ischemic episode with ST-segment depression is seen in Figure 1. Frequency-modulated dual-channel recordings were used over 24

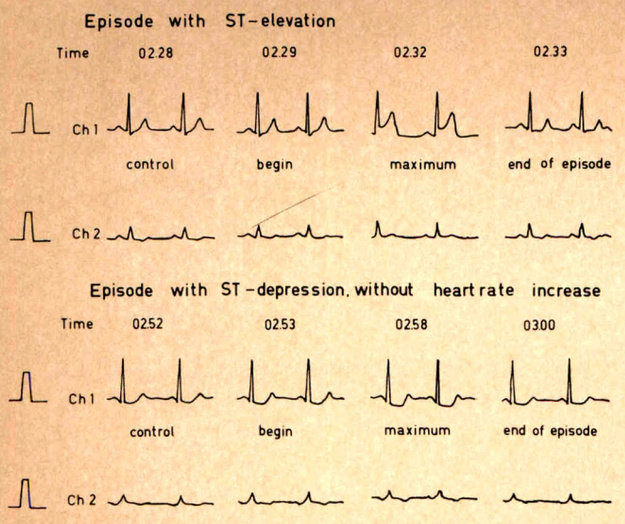

FIGURE 1. Examples of transient ischemic episodes as recorded with frequency-modulated ambulatory electrocardiographic monitoring. With visual analysis, episodes are detected and an example of the electrocardiogram before, at the beginning, at maximal ST deviation and at the end of the episode is documented. Episodes are counted when the ST deviation is >1 mm (0.1 mV) for more than 1 minute.

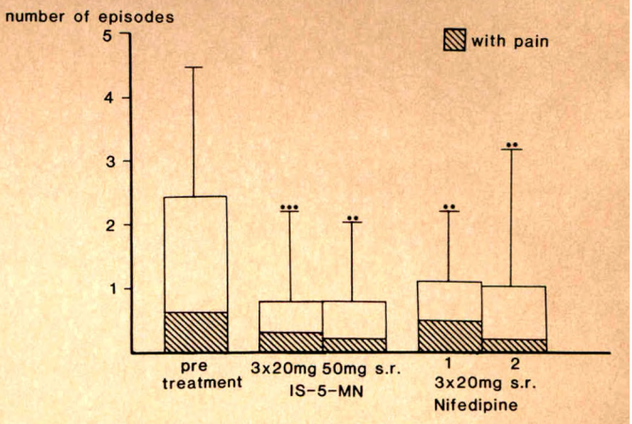

FIGURE 2. Comparison of the frequency of transient ischemic episodes in 15 patients with coronary heart disease before treatment and during 4 randomized weeks of treatment with isosorbide-5-mononitrate or nifedipine. For the patients as a group there is a significant reduction in the frequency of ischemic episodes, which is similar for painful and painless ischemia. s.r. = sustained release.

hours on an Oxford Medilog 2 system with visual analysis. Episodes were identified and examples of the beginning of the episode, 1 minute before the episode, maximal ST changes and the end of the episode were documented. Ischemic ST-segment deviations of >1 minute and >1 mm from the baseline ECG complex were counted as episodes (calibration 10 mm for 1 mV).

Study protocol: Patients were treated in a double-blind crossover randomized fashion for 4 periods of 1 week each. There were 2 periods during which patients received 20 mg nifedipine 3 times daily in sustained-release form. One treatment period consisted of 20 mg of IS-5-MN administered 3 times daily and 1 period consisted of the drug in sustained-release form, 50 mg once daily. Repeated ambulatory ST-segment monitoring for 24 hours was performed at the end of each weekly treatment period. Patients had an event button to mark anginal pain on the ECG recorders and they were asked at the end of each recording period for the number of occurrences of anginal pain and the possible adverse effects of the treatment.

Statistical evaluation: Results between different treatment periods and the period without treatment were compared by the Wilcoxon rank-sum test. Results were considered significant at $p < 0.05$.

Results

During all treatment periods the number of transient ischemic episodes decreased significantly. There were no significant differences between mononitrate and calcium antagonist treatment. The proportion of symptomatic ischemic episodes was 25% during the treatment period and did not change significantly. Therefore, effects of both drugs on symptomatic and asymptomatic episodes of myocardial ischemia were similar (Fig. 2). The large standard deviations seen in Figure 2 show a considerable variability of response.

The total duration of ischemic episodes was also significantly reduced during all treatment periods, from 52 minutes in the pretreatment period to 16 and 17 minutes during treatment with IS-5-MN and 18 and 25 minutes in the nifedipine treatment period. We developed an ischemia score compiling the millimeters of ST depression multiplied by the minutes for each episode. With this ischemia score, the severity of the "total ischemic burden" can be compared between different periods of observation. The score was also significantly reduced during 3 treatment periods in our patients. During 1 of the 2 nifedipine periods the reduction was not significant ($p = 0.075$). However, there was great variability in the responses (Table I). In Table I, the ischemia score is given for each patient and each treatment period. Different types of responses occurred. Some patients had a complete response with both treatments (patients 7, 14, 15 and 18). Some patients responded only to mononitrate (patients 9 and 20). Some patients responded only to nifedipine (patient 16). Others were partial responders, and 1 patient (patient 4) must be considered a nonresponder to both ways of treatment. Thus, the overall response of our group of patients, shows a wide variety of responses, which can be basically different between individual patients.

Discussion

To test the anti-ischemic efficacy of drug treatment, exercise testing has been used most often. Exercise testing with ECG or radionuclide markers of ischemia has the advantage of a clear-cut test situation, in which at least the mode of testing can be standardized and

easily reproduced. This leads to a reasonable reproducibility of exercise test results.[7] In recent years, however, cardiologists have become increasingly aware of the dynamic nature of coronary stenoses that produce ischemia and of the importance of ischemia occurring with or without angina in some patients at very variable degrees of physical activity.

It seems logical therefore to test drugs, which are known for their antianginal effects, with a method that is able to detect myocardial ischemia independently of exercise throughout a 24-hour day. Ambulatory ECG monitoring can be used for this purpose. However, this approach has the definite drawback of a high degree of variability in the occurrence of transient spontaneous ischemic episodes.[8,9] On the other hand, ambulatory monitoring is the only method to date that is widely applicable and can follow the patient for any signs of ischemia when he is out of the hospital and not in an exercise testing environment.

This study tried to overcome the problems of variability by a randomized crossover design that enabled us to compare 2 periods of treatment with mononitrate and 2 periods of treatment with the calcium antagonist nifedipine with a pretreatment period. There was a significant beneficial effect of treatment from both drugs in patients who completed the study. This finding applies to the patients as a group and comprises markedly different responses in individual patients. A large number of patients (5 of 20) could not complete the 4-week study period according to the protocol. Only 1 patient had to discontinue medications because of an adverse effect (nitrate headache). However, 2 patients, considered to have stable angina at entry into the study, had unstable angina with an increasing number of attacks of severe rest angina. This finding suggests that patients who appear to have stable angina but do have frequent ischemic episodes on ambulatory monitoring may not really be in a stable phase of their disease.

In our trial, 2 methods of medical treatment of angina were compared: IS-5-MN and isosorbide dinitrate. IS-5-MN has a markedly improved bioavailability when compared with isosorbide dinitrate. It is still a matter of discussion whether the sustained-release formulation of IS-5-MN is preferable from a pharmacodynamic point of view.[10] For patient compliance, however, once-daily dosage is of great advantage.

Studies from our group and others[4,11,12] have shown that there are no ECG features, heart rate differences or differences in duration of episode, that would allow a clear distinction between symptomatic and silent ischemic episodes. Thus, one would assume that drugs known to be effective for symptomatic episodes should be just as effective for episodes of silent ischemia. In this study, painful and painless ischemic episodes were reduced in parallel fashion. Other investigators have also reported effective reduction of symptomatic and asymptomatic ischemic episodes.[13,14] In this study, IS-5-MN was as effective as nifedipine in reducing ischemic episodes. These results are in keeping with other studies comparing isosorbide dinitrate and nifedipine therapy.[15-18] However, a considerable number of our patients are not treated satisfactorily with either drug alone, and therefore a combination of treatments may be preferable.

TABLE I ST-Segment Score (mm × min)

Pt.	Before Treatment	IS-5-MN 20 mg (tid)	IS-5-MN 50 mg	Nifedipine (20 mg tid) 1	Nifedipine (20 mg tid) 2
1	102	96	36	162	0
2	323*			9	
3	138	0	140	0	0
4	299	120	50	66	231
5	27	8	64	19	12
6	162	11	50	50	64
7	28	0	0	0	0
8	8	0	0	15	0
9	38	0	0	26	12
10	9†			0	
11	11‡		0		
12	5*				
13	174	0	0	45	0
14	97	0	0	0	0
15	94	0	0	0	0
16	6	38	24	0	0
17	33	32	0	106	24
18	35	0	0	0	0
19	138§				
20	24	0	0	118	66

* Discontinued—unstable angina pectoris.
† Discontinued—hypertensive crisis.
‡ Discontinued—thyrotoxicosis.
§ Discontinued—headache.
IS-5-MN = isosorbide-5-mononitrate.

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Comparative Evaluation of Isosorbide-5-Mononitrate and Nitroglycerin in Chronic Congestive Heart Failure

ADAM SCHNEEWEISS, MD

The hemodynamic effects of isosorbide-5-mononitrate (IS-5-MN) and nitroglycerin were compared in 10 patients with chronic congestive heart failure (CHF). Both drugs were given intravenously, at an infusion rate individually titrated to achieve a maximal increase in cardiac output and a maximal decrease in pulmonary capillary wedge pressure. Both drugs produced the typical hemodynamic responses to nitrates, the most prominent of which were decreases in pulmonary capillary wedge, pulmonary arterial and right atrial pressures, and an increase in cardiac output. Several differences in the response to these 2 drugs were observed. Pulmonary capillary wedge pressure was reduced from 31.5 ± 3.0 to 19.6 ± 5.0 mm Hg with nitroglycerin and to 15.0 ± 3.12 mm Hg with IS-5-MN. Both the absolute and the percent decrease with IS-5-MN were significantly greater ($p < 0.05$) than those observed with nitroglycerin. Mean systemic arterial pressure was reduced from 89.2 ± 11.3 to 79.8 ± 10.8 with IS-5-MN (difference not significant) and to 67.5 ± 7.7 mm Hg with nitroglycerin ($p < 0.01$). The difference, both in absolute and percent reductions, was statistically significant. Thus, in patients with chronic CHF, IS-5-MN produced a greater decrease in pulmonary capillary wedge pressure (the major beneficial effect of nitrates in this condition) and a smaller decrease in systemic arterial pressure (the potentially deleterious effects of nitrates). These findings indicate a potential advantage of IS-5-MN over nitroglycerin in patients with CHF, particularly in those with CHF of ischemic etiology.

(Am J Cardiol 1988;61:19E–21E)

Isosorbide-5-mononitrate (IS-5-MN) is a metabolite of isosorbide dinitrate that possesses pharmacologic activity qualitatively similar to that of the parent drug, and a more predictable pharmacokinetic profile.[1–5] It was found effective in all indications for which nitrates are used including congestive heart failure (CHF).

One of the problems associated with nitrate therapy in patients with CHF is that the beneficial reduction in left ventricular filling pressure may be associated with an excessive decrease in systemic vascular resistance. This could be particularly deleterious in patients with coronary artery disease. Preliminary studies revealed that IS-5-MN may have a hemodynamic profile somewhat different from that of nitroglycerin. It may have a greater selectivity to capacitance vessels than to resistance vessels, compared with nitroglycerin. This study compares the hemodynamic responses to IS-5-MN and nitroglycerin in patients with chronic CHF.

From the Geriatric Cardiology Research Foundation, Tel Aviv, Israel.

Address for reprints: Adam Schneeweiss, MD, The Geriatric Cardiology Research Foundation, 9 Kehilat Sofia, 69018 Tel Aviv, Israel.

Methods

Patients: Ten patients (7 men and 3 women, mean age 68 ± 12 years) with chronic CHF were studied. The cause of heart failure was old myocardial infarction in 8 patients and dilated cardiomyopathy in 2. All patients signed an informed consent before the study.

Protocol: The patients were hospitalized in an intensive coronary care unit. All cardioactive drugs were gradually discontinued. A Swan-Ganz catheter was inserted and hemodynamic measurements were ob- tained at rest 2 hours after insertion. Heart rate, temic, pulmonary arterial, right atrial and pul- capillary wedge pressures and cardiac were measured and systemic and pulmonary sis- tance were calculated. IS-5-MN was travenously in 5 patients, and nitr maining 5. The initial infusion and it was individually titrate increase in cardiac output an mean pulmonary capillary w

modynamic measurements were obtained at the time of maximal response (which was achieved in all patients within 24 hours), the drugs were gradually discontinued and the patients were allowed to stabilize at the pretreatment hemodynamic condition. They were then crossed over to the other drug and the same procedure was repeated.

The absolute changes in hemodynamic parameters, the percent changes in these parameters and the levels achieved at maximal therapy were compared. Paired *t* test was used to determine statistical significance.

Results

The doses that achieved maximal effect were 6.5 mg/hour for IS-5-MN and 6.0 mg/hour for nitroglycerin. Control hemodynamic parameters were similar in the pretreatment and stabilization periods, after discontinuation of the drugs in the first phase and before crossover to the other drug.

IS-5-MN significantly reduced diastolic systemic arterial, right atrial, systolic, diastolic, mean pulmonary arterial and pulmonary capillary wedge pressures and pulmonary vascular resistance, and increased cardiac output. Nitroglycerin produced qualitatively comparable effects, except for the decrease in pulmonary vascular resistance, which was nonsignificant. In addition, nitroglycerin, but not IS-5-MN, decreased systemic systolic blood pressure (Tables I and II). This effect on systolic blood pressure was 1 of the 2 major differences between both drugs. Mean systemic

TABLE I Hemodynamic Effects of Isosorbide-5-Mononitrate (IS-5-MN) and Nitroglycerin

	Before Treatment	IS-5-MN	p	Nitroglycerin	p
HR (beats/min)	81.5 ± 9.5	78.1 ± 1.6	NS	80.7 ± 5.9	NS
SBP (mm Hg)	117.8 ± 16.8	108.1 ± 13.2	NS	87.5 ± 10.9	<0.05
DBP (mm Hg)	75.0 ± 8.8	65.6 ± 11.0	<0.05	57.5 ± 6.6	<0.01
MBP (mm Hg)	89.2 ± 11.3	79.8 ± 10.8	NS	67.5 ± 7.7	<0.01
RAP (mm Hg)	17.6 ± 4.9	7.7 ± 3.8	<0.01	6.25 ± 3.6	<0.005
SPAP (mm Hg)	77.5 ± 14.1	49.6 ± 8.9	<0.01	53.6 ± 15.1	<0.01
DPAP (mm Hg)	31.1 ± 2.6	15.5 ± 4.0	<0.01	22.1 ± 5.9	<0.05
MPAP (mm Hg)	46.5 ± 5.6	26.8 ± 5.4	<0.001	32.6 ± 8.4	<0.05
PCWP (mm Hg)	31.5 ± 3.0	15.0 ± 3.12	<0.01	19.6 ± 5.0	<0.01
CO (liters/min)	3.4 ± 0.4	4.4 ± 0.7	<0.05	4.1 ± 0.8	<0.05
SVR (dynes s cm^{-5})	1,705.6 ± 353.4	1,327.1 ± 169.2	NS	1,243.9 ± 252.0	NS
PVR (dynes s cm^{-5})	365.2 ± 161.8	224.5 ± 63.8	<0.05	283.5 ± 179.9	NS

CO = cardiac output; DBP = diastolic blood pressure; DPAP = diastolic pulmonary arterial pressure; HR = heart rate; MBP = mean blood pressure; MPAP = mean pulmonary arterial pressure; NS = not significant; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SBP = systolic blood pressure; SPAP = systolic pulmonary arterial pressure; SVR = systemic vascular resistance.

TABLE II Absolute and Percent Changes in Hemodynamic Parameters

	IS-5-MN		Nitroglycerin		p*	
	Absolute	%	Absolute	%	Absolute	%
MBP (mm Hg)	9.5 ± 10.0	9.8 ± 11.2	20.8 ± 9.46	22.8 ± 9.1	0.01	0.01
MPAP (mm Hg)	19.7 ± 8.6	41.0 ± 15.1	13.6 ± 10.1	28.3 ± 19.1	0.05	0.01
PCWP (mm Hg)	16.5 ± 4.6	51.8 ± 10.8	11.6 ± 6.2	36.4 ± 18.0	0.05	0.05
SVR (dynes s cm^{-5})	378 ± 355	29.9 ± 20.0	437 ± 399	40.3 ± 11.5	NS	0.01
PVR (dynes s cm^{-5})	140 ± 169	24.7 ± 10.9	82 ± 47	40.0 ± 25.2	NS	0.05

* Difference between the effects of both drugs.
Abbreviations as in Table I.

blood pressure was reduced by 9.8% with IS-5-MN and by 22.8% with nitroglycerin. The difference was statistically significant ($p < 0.01$). Moreover, the percent reduction in systemic vascular resistance was significantly greater with nitroglycerin than with IS-5-MN.

In the presence of this greater decrease in arterial pressure with nitroglycerin, this drug reduced the mean pulmonary arterial pressure less than IS-5-MN (28.3 ± 19.1% and 41.0 ± 15.1%, respectively; $p < 0.01$).

Discussion

Our findings indicate that the hemodynamic response to IS-5-MN in patients with chronic CHF resembles, in general, the response to other nitrates.[6-9] The main effect is a decrease in left ventricular filling pressure, which is associated with some increase in cardiac output. However, when compared with nitroglycerin, important quantitative differences in the hemodynamic profile have been observed. The decrease in left ventricular filling pressure was greater and the filling pressure achieved was lower with IS-5-MN than with nitroglycerin. This was found in the presence of a greater reduction in systolic and mean blood pressures, and achievement of lower systolic and mean blood pressures with nitroglycerin compared with IS-5-MN (all differences statistically significant). The cause of this difference is not known.

This hemodynamic profile of IS-5-MN determines its clinical use, provides a safety factor in treatment of certain patients and allows some selectivity of nitrate therapy in various conditions. Obviously IS-5-MN is most suitable for treatment of patients with CHF who mainly have symptoms of pulmonary congestion. This drug may be safer than nitroglycerin in patients with heart failure of ischemic etiology, because it is less likely to lower the coronary perfusion pressure excessively. It is important to confirm this hypothesis in patients with acute-onset heart failure complicating acute myocardial infarction.

Rabinowitz et al[10] studied the hemodynamic effects of intravenous IS-5-MN in 17 patients with CHF complicating an acute (10 patients) or old (7 patients) myocardial infarction. The infusion rate was titrated to achieve maximal effects. The maximal doses used reduced mean pulmonary capillary wedge pressure from 25.4 ± 4.6 to 18.3 ± 5.9 mm Hg, right atrial pressure from 9.1 ± 5.6 to 6.3 ± 4.2 mm Hg, and systemic vascular resistance from 1,778 ± 426 to 1,610 ± 298 dynes s cm^{-5}.

The effect of IS-5-MN in the patient with acute or chronic CHF was comparable to that found in our patients. Thus, the differences between IS-5-MN and nitroglycerin found in our study may also be observed in acute-onset CHF.

Moreover, Rabinowitz et al[10] found a greater response of systemic vascular resistance in patients with chronic heart failure than in those with acute heart failure. This suggests that the advantages of IS-5-MN may be more prominent in acute CHF.

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Emergency Treatment of Severe Cardiogenic Pulmonary Edema with Intravenous Isosorbide-5-Mononitrate

CHARLES HARF, MD, and ROBERT WELTER, MD

Intravenous isosorbide-5-mononitrate (IS-5-MN) was administered to 24 patients, mean age 73, with severe respiratory distress after pulmonary edema and acute left heart failure. The condition was due to ischemic cardiopathy in 18 patients (4 with acute myocardial infarctions), congestive cardiomyopathy in 3, hypertensive cardiopathy in 2, and mitral valvular disease in 1. Therapy consisted of an intravenous (i.v.) bolus dose of IS-5-MN, followed by a continuous infusion (mean 8 mg/hour over 24 hours) of i.v. furosemide and additional oxygen. Clinical data were recorded as well as blood gas values and repeated chest radiographs. All patients survived and improved markedly; only 6 needed mechanical ventilation. Most patients had fast respiratory relief, with no untoward reaction, except a brief decrease of blood pressure in a ventilated patient taking morphine. These data indicate that i.v. IS-5-MN is effective and safe for the management of severe acute cardiogenic pulmonary edema.

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Acute pulmonary edema after left ventricular failure represents a life-threatening medical emergency dominated by respiratory distress and hypoxemia. The treatment is aimed at a prompt reduction of the increased capillary pulmonary wedge pressure, responsible for a transudation of fluid in the alveoli.[1]

Nitrates are potent venodilators and consistently lower left ventricular filling pressure by venous pooling. Although nitrates are predominantly preload-reducing agents, they are able to cause a decrease in systemic vascular resistance and an increase in cardiac output.[2–4] Parenteral administration seems preferable in the critically ill to achieve therapeutic levels in the shortest time, the continuous infusion permitting a precise, homogenous dosage. Intravenous (i.v.) isosorbide dinitrate (ISDN) has been shown to be a valuable and safe treatment in acute left pump failure.[5–8] Isosorbide-5-mononitrate (IS-5-MN) is the main metabolite of ISDN, sharing similar pharmacologic activity, with a clearer pharmacokinetic profile.[9] To assess the efficacy, tolerability and safety of i.v. IS-5-MN, we undertook an open, clinical study in 24 patients admitted to our intensive care unit with acute cardiogenic pulmonary edema.

From the Centre Hospitalier of Luxembourg, Grand Duchy of Luxembourg, West Europe.

Address for reprints: Charles Harf, MD, Réanimation Médicale, Centre Hospitalier de Luxembourg, Luxembourg, West Europe.

Methods

Patients: We studied 24 consecutive patients (14 men and 10 women, aged 56 to 88 years [mean 72]) admitted to the intensive care unit for respiratory distress related to acute left heart failure with pulmonary edema (Table I). Acute left ventricular failure was clinically manifest. All patients had extreme dyspnea, cyanosis, gallop rhythm and extended lung crepitations (with frothy sputum in 17). Arterial blood gases showed marked hypoxemia, and there was radiologic evidence of extended interstitial and alveolar edema and cardiomegaly. Most patients had not responded to previous diuretic therapy. Patients were excluded from the study because of shock, systemic hypotension (systolic blood pressure <100 mm Hg), a major renal insufficiency, or when long-acting nitrates had been administered during the last 24 hours.

The cause of acute failure was acute myocardial infarction in 4 patients (3 anterior, 1 inferior localization) and chronic ischemic cardiopathy with recurrent myocardial infarctions in 14 (6 with hypertension). In the remaining 6 patients, 3 had congestive cardiomyopathy, 2 hypertensive cardiopathy and 1 mitral valve disease.

Procedure: Baseline measurements of respiratory rate, heart rate, and systolic and diastolic blood pressures were recorded, the mean arterial pressure being calculated as follows: MP = DP + 1/3 (SP − DP) mm Hg, where MP = mean arterial pressure, DP = diastolic pressure, and SP = systolic pressure. The grade of dyspnea and the extent of wet rales were assessed and noted from 0 to ++++.

Blood gases: Hydrogen ion concentration, $paCO_2$ and paO_2 were determined from arterial blood without additional oxygen (ABL 2 Radiometer). A bedside chest radiograph showed the grade of cardiomegaly and the extent of interstitial and alveolar edema. After starting therapy, clinical data were collected after 0.5, 1, 2, 4, 6, 9, 12, 18 and 24 hours. The hourly diuresis was measured by a vesical catheter. Blood gas values were controlled at 2, 4, 6, 12, 18 and 24 hours, while the thorax radiograph was repeated after 6, 12 and 24 hours.

IS-5-MN administration began with an i.v. bolus dose of 10 mg, repeated after 10 minutes if necessary and followed by a continuous infusion of 1 mg/ml concentration for 24 hours. The rate ranged from 4 to 15 mg/hour, depending on the weight and condition of the patients. Additional therapy, oxygen and i.v. furosemide, was administered to all patients. Digoxin, theophyllin and antiarrhythmic therapy was administered when necessary.

Statistical methods: Statistical evaluation of data was done by means of exploratory data analysis according to the design of the study as an open clinical trial without randomization. Values after infusion of i.v. IS-5-MN were compared with baseline values by means of the Wilcoxon-Pratt signed-rank test.

Results

Therapy: Therapy consisted of a bolus dose of IS-5-MN (mean 13.45 ± 8.14 mg). The infusion rate was 8.08 ± 3.71 mg/hour for 6 hours, 7.89 ± 2.85 mg/hour for 24 hours or 0.12 mg/kg/hour. The mean dose of furosemide was 53.91 ± 28.56 mg at 6 hours and 63.48 ± 27.4 mg at 12 hours. Most patients were given 40 mg i.v. at the beginning of the study (except in 6 cases, in which administration was delayed for 2 hours) (Table II). Six patients received theophyllin because of bronchospasm; another 6 received digoxin for tachyarrhythmia. Amiodarone and lidocaine were administered 5 times.

All patients survived and could be dismissed from the intensive care unit within 48 hours with oral IS-5-MN. Only 6 needed mechanical ventilation, 5 immediately after admission because of extreme asphyxia, coma or respiratory arrest, and the sixth, an 88-year-old woman, after 9 hours of therapy because of aspiration of vomitus. The duration of intubation ranged from 9 to 27 hours (mean 17.5). The 18 nonventilated patients had marked symptomatic improvement and, despite initial severe respiratory distress, avoided mechanical ventilation. Fourteen of them had a rapid relief of dysnpea (within 5 to 10 minutes after a bolus injection) with color returning to the extremities. In the remaining 4, respiratory amelioration occurred after

TABLE I Patient Characteristics at Admission

Pt. No.	Age (yr) & Sex	Diagnosis	Dyspnea	Wet Rales	Blood Gases			Radiologic Edema
					pH	$paCo_2$ (torr)	paO_2 (torr)	
1	68M	HC	++++	+++	—	—	—	++++
2	88F	IC	++++	++++	7.17	48.2	34.0	+++
3	71M	IC	++++	++++	7.23	44.3	48.8	+++
4	64M	IC	++++	++++	7.04	78.5	51.1	+++
5	73M	AMI + HT	++++	++++	7.10	45.9	55.0	+++
6	72M	IC + HT	++++	++++	7.17	66.9	36.9	+++
7	87F	IC + HT	+++	++++	7.38	40.6	59.1	+++
8	72M	IC + HT	++++	++++	7.27	39.1	58.5	++++
9	76M	IC	++++	+++	7.27	39.5	51.0	+++
10	65F	MVD	+++	+++	7.44	39.0	64.9	+++
11	77F	IC	++++	++++		MV		+++
12	56M	CC	++++	++++	7.15	53.7	57.0	+++
13	69F	AMI	++++	++++	7.29	36.7	48.0	+++
14	70F	IC + HT	+++	++++	7.38	35.5	49.0	+++
15	72M	CC	++++	++++	7.34	40.2	61.0	+++
16	88M	IC	++++	+++	7.46	25.6	53.0	+++
17	86F	IC	++++	++++	7.16	37.1	45.0	+++
18	69M	IC + HT	+++	++	7.38	42.2	61.0	++
19	79F	AMI	+++	+++	7.23	55.4	49.0	+++
20	79M	IC	++++	++	7.41	39.0	61.0	++
21	66F	HC	MV	++++		MV		+++
22	67M	CC	++++	++++	7.25	40.4	56.0	++
23	58M	IC	++++	++++	7.12	65.6	50.0	+++
24	75F	AMI	+++	+++	7.36	40.6	50.0	+++

AMI = acute myocardial infarction; CC = congestive cardiomyopathy; HC = hypertensive cardiopathy; HT = arterial hypertension; IC = ischemic cardiopathy; MVD = mitral valve disease; MV = patient was already under mechanical ventilation at admission; ++++ = very strong or extended; +++ = strong or extended; ++ = moderate; + = slight; 0 = absent.

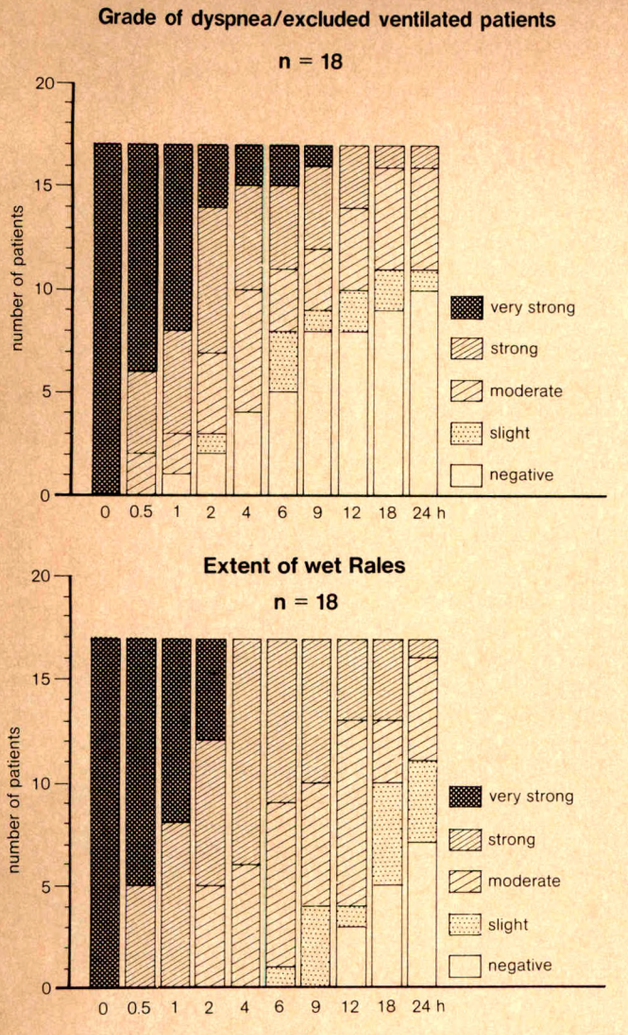

FIGURE 1. Grade of dyspnea and extent of wet rales at pulmonary auscultation over the 24-hour study period.

TABLE II Therapy

IS-5-MN dosage (n = 24)		
Bolus:	13.54 ± 8.14 mg	
Infusion rate:	8.13 ± 3.70 mg/hour over	2 hours (from 0–2 hours)
	8.15 ± 3.75 mg/hour over	4 hours (from 0–4 hours)
	8.08 ± 3.71 mg/hour over	6 hours (from 0–6 hours)
	7.93 ± 3.20 mg/hour over	12 hours (from 0–12 hours)
	7.89 ± 2.85 mg/hour over	24 hours (from 0–24 hours)
	= 0.12 ± 0.05 mg/kg/hour	
Furosemide dosage (n = 23)		
	53.91 ± 28.56 mg over	6 hours (from 0–6 hours)
	55.65 ± 29.52 mg over	9 hours (from 0–9 hours)
	63.48 ± 27.40 mg over	12 hours (from 0–12 hours)
	72.17 ± 33.43 mg over	18 hours (from 0–18 hours)

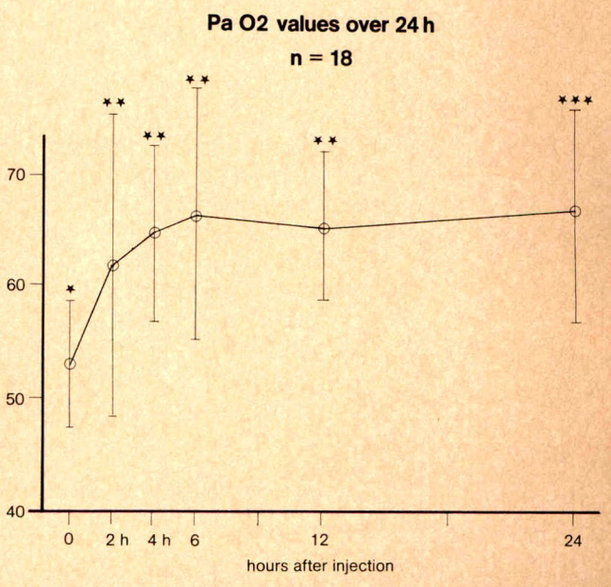

FIGURE 3. Partial arterial oxygen pressure (PaO_2) over the 24-hour study period (in torr) excluding the ventilated patients. *p <0.05; **p <0.01; ***p <0.001 compared with baseline values.

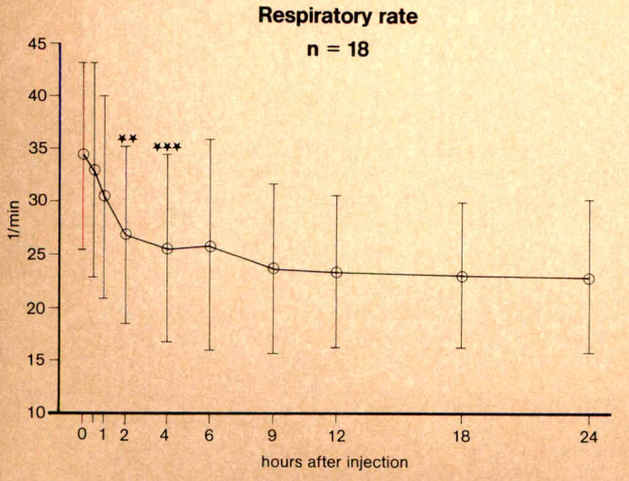

FIGURE 2. Respiratory rate over the 24-hour study period, excluding the ventilated patients. *Bars*, standard deviation. **p <0.01; ***p <0.001 compared with baseline values.

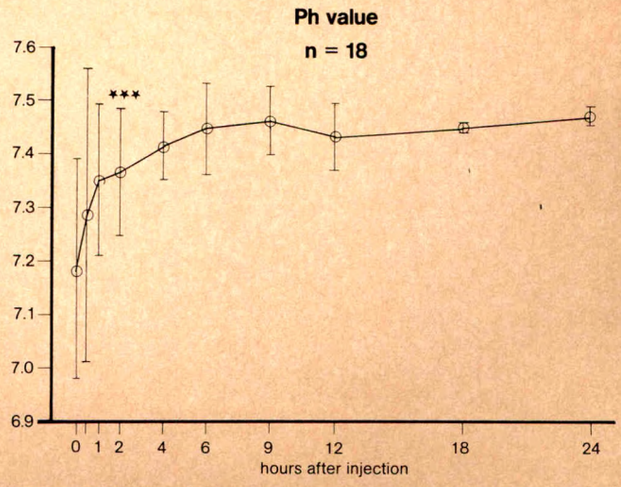

FIGURE 4. Hydrogen ion concentration (Ph) over the 24-hour study period, excluding ventilated patients. *** p <0.001 compared with baseline values.

90 minutes. A marked regression of the grade of dyspnea appeared within 2 hours, with similar decline of the lung crepitation (Fig. 1).

Mean respiratory rate decreased from 36 ± 7 cycles/min before treatment to 27 ± 8 cycles/min at 2 hours (−22.9%, $p < 0.001$), with further reduction at 9 hours (Fig. 2). Baseline blood gas values showed marked hypoxemia in all nonventilated patients: paO_2 53.9 ± 5.7 torr. A significant improvement to 61.8 ± 13.4 torr occurred at 2 hours ($p < 0.01$), with little further change. The increase from baseline to that at 24 hours was highly significant ($p < 0.001$) (Fig. 3). Acidosis (pH <7.30) was present in 13 patients. Mean values increased from a pH of 7.214 ± 0.12 to a pH of 7.39 ± 0.058 at 2 hours ($p < 0.001$) without bicarbonate administration (Fig. 4). Thirteen patients were hypercapnic at admission ($paCO_2 > 40$ torr). $PaCO_2$ decreased from 48 ± 10.4 to 34.4 ± 7.7 torr at 2 hours (−23.9%, $p < 0.001$) (Fig. 5). Heart rate decreased from 118 ± 19 to 105 ± 19 beats/min at 1 hour (−11%, $p < 0.001$), stabilizing under 100 beats/min at 2 hours (Fig. 6).

Systemic blood pressure: Systemic, diastolic and mean arterial pressures decreased significantly at 1 hour with mean pressure decreasing from 124 ± 28 to 112 ± 15 mm Hg (−9.7%, $p < 0.01$); difference with baseline values was maximal at 6 hours (−16.1%, $p < 0.001$) (Fig. 7). Mean arterial pressure decreased in patients with high initial values, but was not affected in the others (Fig. 8). A rapid onset of marked diuresis occurred in all patients in combination with i.v. furosemide (1,000 ml was reached at 4 hours) (Fig. 9). The degree of radiographic pulmonary edema improved in all patients throughout the subsequent 24 hours of therapy.

Adverse effects: Blood pressure decreased to 80/60 mm Hg, with a decrease in diuresis at 20 minutes in 1 patient ventilated at admission when 10 mg of i.v. morphine had been given because of agitation. After discontinuing IS-5-MN infusion, blood pressure increased to 100/65 mm Hg at 1 hour with new onset of diuresis. No other untoward incident was noted. The 4 patients with acute myocardial infarctions had fast relief of pain and their course was uncomplicated. There was no complaint of headache.

Discussion

Severe pulmonary edema in acute left ventricular failure represents a critical situation that demands prompt resolution. Hemodynamically, systemic arterial pressure is often elevated and cardiac output may be decreased to such an extent that systemic vascular resistance is increased. Left venricular end-diastolic and pulmonary capillary pressures are strikingly increased, leading to transudation of fluid in the alveoli with resultant respiratory distress,[10] The major objective of treatment is the rapid reduction of left ventricular filling pressure.

Nitrates offer substantial advantages over conventional diuretic drugs[11] and phlebotomy and thus appear to be the drug of choice.[5,12–14] They consistently reduce left ventricular filling pressure by potent venodilation and venous pooling. In patients with severe heart failure, they increase cardiac output by decreas-

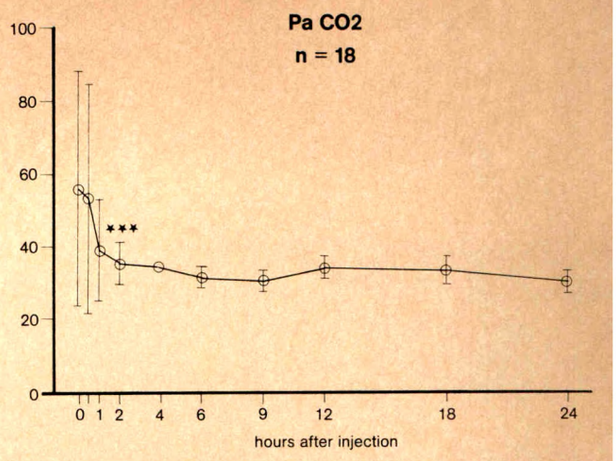

FIGURE 5. Partial arterial CO_2 pressure ($PaCO_2$) over the 24-hour study period (in torr), excluding ventilated patients. ***p <0.001 compared with baseline values.

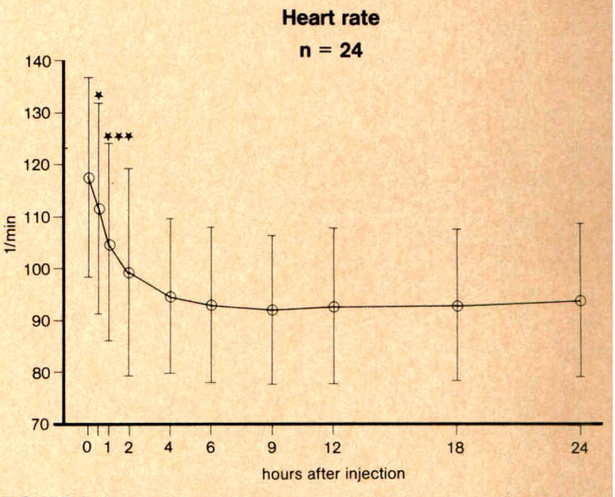

FIGURE 6. Heart rate over the 24-hour study period. *p <0.05; ***p <0.001 compared with baseline values.

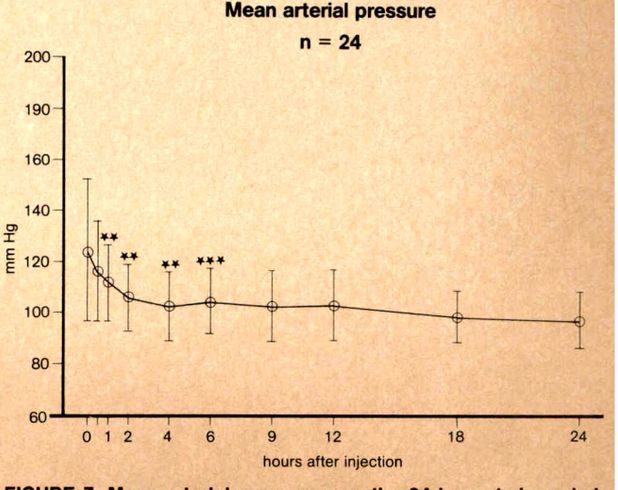

FIGURE 7. Mean arterial pressure over the 24-hour study period. **p <0.01; ***p <0.001 compared with baseline values.

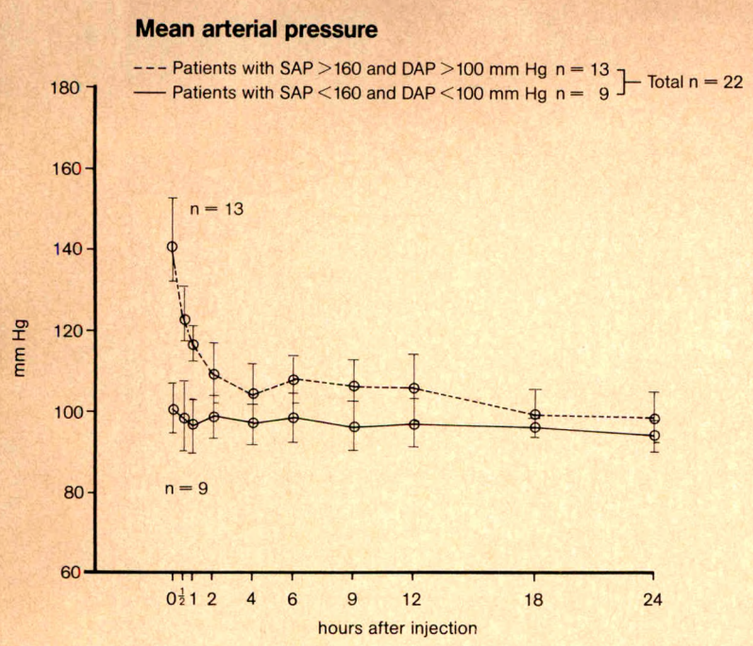

FIGURE 8. Mean arterial pressure over the 24-hour study period in hypertensive and normotensive patients. Hypertensive patients: systolic pressure (SAP) >160 mm Hg; diastolic pressure (DAP) >100 mm Hg; Normotensive patients: SAP <160 mm Hg; DAP <100 mm Hg.

ing systemic vascular resistance. In patients with ischemic heart disease, they improve parietal dyskinesia by parietal tension reduction and improve regional myocardial perfusion, and in those with mitral valvular insufficiency, nitrates decrease regurgitant blood volume.[1,2,4,15]

One of the major problems in nitrate therapy is the risk of severe arterial hypotension after an excessive decrease in systemic vascular resistance, with aggravation of ischemic heart disease.[2]

Parenteral administration is a logical course of therapy in the very ill patient, because of rapid onset of action and avoidance of the uncertainties of tolerance and absorption.

In patients with acute pump failure, nitroglycerin and i.v. ISDN have been widely used, with great benefit.[6–8,11] IS-5-MN, the main metabolite of ISDN, has qualitatively similar pharmacologic activity, but offers a longer elimination half-life, better predictability and good correlation between pharmacokinetics and effects.

In patients with severe acute pulmonary edema, therapeutic levels have to be achieved in the shortest time possible. For this reason, an initial i.v. bolus dose was used, followed by continuous infusion of concentrated IS-5-MN, permitting precise dosage and homogenous plasma levels, with a reduced fluid intake.[16] The aim of this open clinical trial was to assess the value and efficacy of this mode of administration of IS-5-MN and its safety of use in the daily practice. It is not often practical or possible to place a Swan-Ganz catheter in the pulmonary artery before starting therapy in patients with extreme dyspnea. Therefore, diagnosis of acute pump failure was established on clinical ground with the monitoring of blood gas, and electrocardiographic and radiologic changes; therapy was administered under clinical monitoring. Our elderly patients were all in very critical condition, representing a particularly severe selection of acute left ventricular failure, as seen on the baseline clinical, blood gas and radiologic findings. The results demonstrate the efficacy and tolerability of i.v. IS-5-MN.

All patients had marked symptomatic improvement with IS-5-MN; only 6 had to be ventilated. A prompt relief of dyspnea often followed the initial bolus. In the 4 nonventilated patients, in whom regression of dyspnea was slower, 2 major bronchospasms and 1 acute bronchitis were noted. A rapid improvement of arterial oxygenation is required in these presentations of pulmonary edema, when severe hypoxemia dominates. A significant increase of paO_2 was seen within 2 hours, permitting hemoglobin saturation of >90%. Metabolic and respiratory acidosis with hypercapnia normalized without additional therapy.

Elevated heart rate and systemic blood pressure decreased to normal values after 1 hour, with marked significance in mean arterial pressure. In patients with initial normal levels, no further decrease of blood pressure or reflex tachycardia occurred. Abrams[2] and Chiche et al[14] demonstrated that nitrates may reduce systemic vascular resistance only if it is initially elevated.

Rabinowitz et al[8] showed a relation between high systemic vascular resistance, tachycardia and elevated levels of circulating cathecholamines in response to low cardiac output. Initial systemic vascular resistance levels may predict the response to nitrate therapy: Cardiac output increases in patients with high initial systemic vascular resistance. Our dates with IS-5-MN demonstrate beneficial effects in patients with elevated blood pressure.

Our study showed that IS-5-MN caused no adverse decrease of blood pressure. A temporary decrease was due to morphine and mechanical ventilation, and was

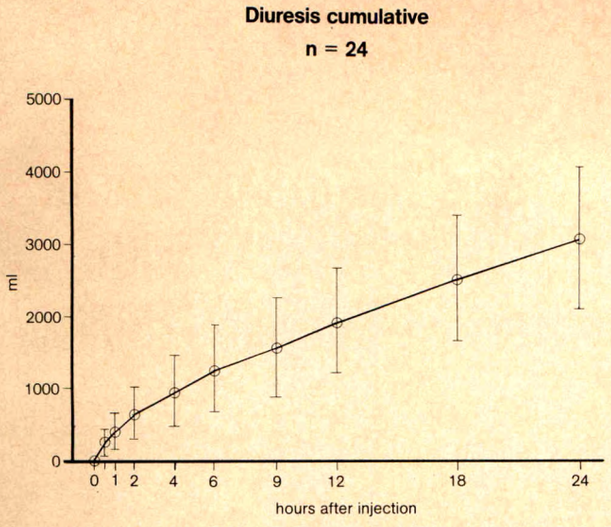

FIGURE 9. Cumulative diuresis over the 24-hour study period.

reversible after less than 1 hour. A marked diuresis with rapid onset of urine flow and negative fluid balance occurred in all patients, many of them having been unresponsive to diuretic therapy before IS-5-MN. ISDN has been shown to increase significantly effective renal perfusion in acute heart failure with a proved synergistic effect with furosemide.[17]

As an open study, conclusions must be limited because of lack of control data. Otherwise, from the ethical point of view, the performance of placebo-controlled studies in such severe ill patients is impossible. In an open hemodynamic trial with i.v. IS-5-MN, Gammage et al[16] demonstrated a rapid decrease of pulmonary capillary pressure associated with symptomatic relief and the lack of other adverse changes, particularly a significant decrease in blood pressure. This confirms that IS-5-MN may be given safely by this route of administration without hemodynamic monitoring.

Conclusions

Intravenous IS-5-MN is effective and safe in the management of acute pulmonary edema, without significant risk of adverse circulatory effects, provided there is close clinical monitoring, particularly regular control of heart rate and blood pressure.

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Dose-Ranging Study of Isosorbide-5-Mononitrate in Chronic Congestive Heart Failure Treated with Diuretics and Angiotensin-Converting Enzyme Inhibitor

NADIA DEBBAS, MD, DAVID WOODINGS, MRCP, CHRISTINE MARKS, ANGELA BHANS, MBBS, AKEEL JUBBER, MRCP, IAN DEWS, MRCP, JOHN STEPHENS, MD, MRCP, and MALCOLM VANDENBURG, BSc, MRCP

The hemodynamic response of isosorbide-5-mononitrate (IS-5-MN) to the addition of the widely used therapy of diuretic drugs and the maximally tolerated dose of enalapril for heart failure was assessed in 8 patients with congestive heart failure (CHF) (New York Heart Association class II and III). The diuretic therapy was furosemide, 40 to 80 mg/day, with or without amiloride, 5 to 10 mg/day. The dose of enalapril was 5 to 20 mg/day. Four hours after the administration of the morning dose of enalapril, a Swan-Ganz catheter was positioned in the pulmonary artery. Patients received increasing doses of IS-5-MN to produce a satisfactory decrease in pulmonary capillary wedge pressure. Two of the first 3 patients studied had a large reduction in blood pressure when given 10 mg of IS-5-MN. Subsequent patients were therefore given an initial dose of 5 mg, the total dose being 5 to 20 mg over 2 hours. Results at baseline and 1 hour after the final dose of IS-5-MN are expressed as mean ± standard deviation. Both pulmonary artery systolic and diastolic pressures decreased significantly ($p < 0.05$) by 12.2 ± 8.9/4.2 ± 5.2 mm Hg, from 47.2 ± 16.0/21.6 ± 6.0 mm Hg to 35.0 ± 15.2/17.4 ± 9.3 mm Hg. Pulmonary capillary wedge pressure decreased by 8.6 ± 4.4 mm Hg, from 22.1 ± 5.4 to 13.6 ± 7.5 mm Hg ($p < 0.01$). There was a significant ($p < 0.05$) decrease in both systolic and diastolic blood pressures of 18.0/9.1 mm Hg, from 111.2 ± 24.5/72.6 ± 4.9 to 93.2 ± 22.1/63.5 ± 8.7 mm Hg. There was no change in heart rate, right atrial pressure and cardiac output.

The results suggest that IS-5-MN produces beneficial hemodynamic effects when added to diuretics and angiotensin-converting enzyme inhibitors. The doses used are lower than when IS-5-MN is added to the diuretic alone.

(Am J Cardiol 1988;61:28E–30E)

Diuretics are widely used as first line treatment of chronic congestive heart failure (CHF). When additional therapy is necessary, the beneficial effect of nitrates is well established.[1] Recently, angiotensin-converting enzyme inhibitors have been used as second line treatment in addition to diuretics.[2]

Oral isosorbide dinitrate has generally been used in patients receiving diuretics plus another additional therapy, with or without digitalis, as a further stage of treatment. However large doses are often required to achieve suitable beneficial effect, although tolerance has not yet been documented even at large doses.[3,4] Isosorbide-5-mononitrate (IS-5-MN), an active metabolite of isosorbide dinitrate, has a similar hemodynamic profile in patients with chronic CHF and may be more potent.[5]

The purpose of this study is to define the dose response in hemodynamic changes in patients with CHF when IS-5-MN is added to their treatment with the angiotensin-converting enzyme inhibitor, enalapril.

From Romford Cardiovascular Research, Department of Cardiology, Oldchurch Hospital, Romford, Essex RM7 OBE, England.

Address for reprints: John Stephens, MD, Department of Cardiology, Oldchurch Hospital, Romford, Essex RM7 OBE, England.

Methods

Patients: Eight patients (6 men and 2 women aged 52 to 78 years [mean 63]) were entered into the study. All patients had New York Heart Association class II and III CHF due to ischemic heart disease. They were

TABLE I Measurements of Pulmonary Artery, Capillary Wedge and Systemic Blood Pressures in Eight Patients Treated with Diuretics and Enalapril*

	0 Hour	1 Hour After First Dose	1 Hour After Last Dose	2 Hours After Last Dose
PA SYS (mm Hg)	47.2 ± 16.2	36.4 ± 16.6†	35.0 ± 15.2†	40.0 ± 19.7†
PA DIA (mm Hg)	21.6 ± 6.0	17.2 ± 9.9†	17.4 ± 9.3†	17.3 ± 8.5†
PCWP (mm Hg)	22.1 ± 5.4	12.9 ± 5.8‡	13.6 ± 7.5‡	14.3 ± 7.9‡
BP SYS (mm Hg)	111.2 ± 24.5	96.4 ± 20.3 (NS)	93.2 ± 22.1†	92.9 ± 14.2†
BP DIA (mm Hg)	72.6 ± 4.9	65.1 ± 10.6 (NS)	63.5 ± 8.7†	62.9 ± 10.5†

* Mean value of systolic and diastolic pulmonary arterial pressures (PA SYS, PA DIA), pulmonary capillary wedge pressure (PCWP) and systolic and diastolic blood pressures (BP SYS and BP DIA) in 8 patients treated with diuretics and enalapril before and 1 hour after the first dose and 1 and 2 hours after the last dose of isosorbide-5-mononitrate.

† $p < 0.05$.

‡ $p < 0.01$.

NS = not significant.

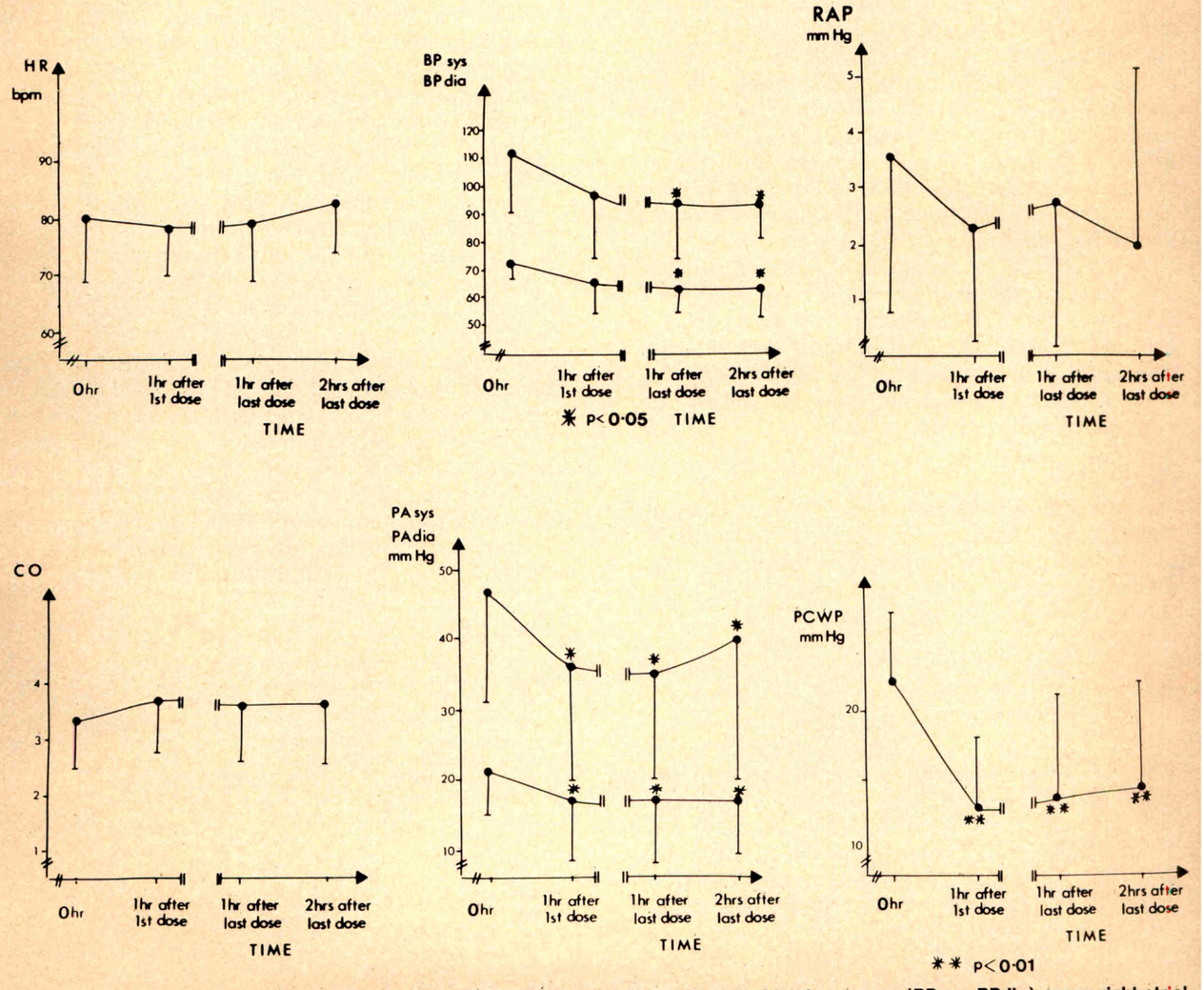

FIGURE 1. Mean value and standard deviation of heart rate (HR), systolic and diastolic blood pressures (BPsys, BPdia), mean right atrial pressure (RAP), cardiac output (CO), systolic and diastolic pulmonary arterial pressures (PAsys, PAdia) and pulmonary capillary wedge pressure (PCWP) in 8 patients treated with diuretics and enalapril before and 1 hour after the first dose of isosorbide-5-mononitrate (5 or 10 mg), and 1 and 2 hours after the last dose of isosorbide-5-mononitrate (5, 10 or 20 mg). * $p < 0.05$; ** $p < 0.01$.

receiving a stable dose of diuretics: furosemide, 40 mg/day (n = 6) and 80 mg/day (n = 2) with or without amiloride 5 mg/day (n = 4) and 10 mg/day (n = 1). They also were taking the maximal tolerated dose of enalapril, 5 to 20 mg/day (5 mg in 1, 10 mg in 3, 15 mg in 1 and 20 mg in 3 patients). Before entering the study, all patients gave informed written consent.

All medications were taken normally until the day of the study when the diuretic was omitted. Four hours after the morning dose of enalapril was administered, hemodynamic evaluation was performed by Swan-Ganz catheterization. Measurements were obtained from midchest level. Baseline measurements of heart rate, systolic and diastolic pulmonary artery, pulmonary capillary wedge and mean right atrial pressures and cardiac output in triplicate using the thermodilution method were obtained. Having confirmed hemodynamic stability, and provided that pulmonary capillary wedge pressure was >16 mm Hg, increasing doses of oral IS-5-MN were given to reduce pulmonary capillary wedge pressure to between 12 and 15 mm Hg.

In the first 3 patients studied, an initial dose of 10 mg was given, followed 60 minutes later by hemodynamic evaluation. In the next 5 patients, the initial dose of IS-5-MN was 5 mg. If systolic blood pressure was maintained at >90 mm Hg and left ventricular filling pressure at >12 mm Hg 60 minutes after dose evaluation, further doses of 5 mg were administered if necessary. Hemodynamic status was assessed 60 minutes after each dose.

Mean values and standard deviation were calculated for each parameter before, 1 hour after the first dose and 1 and 2 hours after the last dose of IS-5-MN was administered. Student paired *t* test was used to compare baseline values with the values at 1 hour after the first dose and 1 and 2 hours after the last dose of IS-5-MN for each variable.

Results

Two of the first 3 patients who received 10 mg of IS-5-MN as an initial dose had a reduction in systolic blood pressure to 60 mm Hg. The third patient had a satisfactory hemodynamic response 1 hour after receiving an additional dose of 10 mg of IS-5-MN (cumulative dose 20 mg). Three of the 5 remaining patients received 5 mg of IS-5-MN, 1 patient received additional doses to a cumulative dose of 15 mg, and 1 patient received additional doses to a cumulative dose of 20 mg. All patients responded over 4 hours. Both systolic and diastolic pressures decreased significantly by 10.8 and 4.4 mm Hg, respectively, between baseline and 1 hour after the first dose of IS-5-MN (Table I) and remained low at 1 and 2 hours after the last dose (Fig. 1). Pulmonary capillary wedge pressure decreased by 9.2 mm Hg 1 hour after the first dose and also remained low at 1 and 2 hours after the last dose. The same type of response was observed for systolic and diastolic pressures, with a decrease of 18.0 and 9.1 mm Hg 1 hour after the last dose of IS-5-MN was administered. There was no change in heart rate, right atrial pressure and cardiac output (Fig. 1).

Discussion

IS-5-MN is a metabolite of isosorbide dinitrate. Unlike the latter, which undergoes considerable biotransformation by the liver and possibly by the gut, IS-5-MN is completely bioavailable.[6] Stephens et al[5] found that acute oral IS-5-MN given to patients with CHF taking diuretics alone has beneficial effects on left ventricular performance through reduction in preload. In the present study, the acute effect of IS-5-MN added to diuretic therapy plus maximal tolerated dose of enalapril was similar, reducing the preload but also decreasing systemic arterial pressures.

In our experience, when patients were taking diuretics plus enalapril, after 3 attempts with initial doses of 10 mg of IS-5-MN, 2 patients had severe hypotension requiring reduction of the first dose. However, in the report by Stephens et al,[5] the doses used to achieve satisfactory hemodynamic changes in patients taking diuretics alone varied between 20 and 100 mg of IS-5-MN, the initial dose being 20 mg. Therefore, the full dose received by our patients was about 20 to 25% of that used in studies where an angiotensin-converting enzyme inhibitor was not part of the successful treatment. This suggests that patients receiving enalapril in addition to diuretics have an increased sensitivity to the vasodilator effect of IS-5-MN and therefore lower doses of the latter should be used. However this reaction seems to be a first-dose effect. We would therefore suggest that 5 mg would be a correct starting dose in this circumstance and that until absolute safety of this dose has been evaluated, it would be appropriate for patients to be kept under medical supervision for at least 4 hours.

Although there is doubt concerning the long-term efficacy of nitrates in patients with angina because of tolerance,[7] there is evidence that tolerance does not develop during long-term treatment with isosorbide dinitrate in patients with CHF[3,4]; the results of previous studies indicate that the same is true for IS-5-MN.[5] However a long-term double-blind study under the same conditions as the present one is still needed to confirm the benefits seen in this pilot study.

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Acute Effect of Various Doses of Isosorbide-5-Mononitrate on Hemodynamic and Exercise Performance in Coronary Artery Disease

WOLFGANG JANSEN, MD, LEONHARD MEYER, MD, and MICHAEL TAUCHERT, MD

The optimal dose of nitrates is still controversial, as chronic usage of too high a dose may result in a decrease in vascular response. The dose should be determined to reduce preload acutely, and not to decrease the activity during chronic therapy. To determine this dose, 50 patients with angiographically confirmed coronary artery disease were studied. The effects on heart rate and mean systemic and pulmonary arterial pressures at rest and during exercise, and work capacity and duration were measured. The patients were classified into 5 groups, receiving placebo or isosorbide-5-mononitrate, 5, 10, 20 and 50 mg, respectively, as a single oral dose. Placebo had no effect on the measured parameters. All doses of isosorbide-5-mononitrate reduced mean pulmonary arterial pressure: 10 mg—by 16% at rest and 24% during exercise; 20 mg—24% and 34%, respectively (a near maximal effect); and 50 mg—27% and 38%. Similar results were found also for work capacity: 10 mg increased work capacity by 33%; 20 mg—79%; and 50 mg—56%. Thus, the therapeutically optimal single dose is about 20 mg. Higher doses produce no additional benefit and increase the risk for tolerance development.

(Am J Cardiol 1988;61:31E–35E)

The accurate dose of either isosorbide dinitrate (ISDN) or isosorbide-5-mononitrate (IS-5-MN) optimally affecting both hemodynamics and exercise performance is not known.[1–5] The possibility of development of tolerance to nitrates due to use of high doses indicates that these drugs should be given at a dose sufficient to produce their therapeutic effect but at a lower dose than that causing tolerance. Dietmann et al[6] demonstrated with animal studies, a linear relation between the nitrate dose, mean plasma concentration and the extent of reducing systolic blood pressure. These findings indicate that it is possible to determine the quantitative relations between the dose of IS-5-MN and its effect. This study determines the acute effect of various doses of IS-5-MN on hemodynamics and exercise performance of patients with coronary artery disease.

From the Medizinische Klinik 1 Kardiologie, Städtisches Krankenhaus, Leverkusen, Federal Republic of Germany.

Address for reprints: Michael Tauchert, MD, Städtisches Krankenhaus, Leverkusen, Medizinische Klinik, Dhünnberg 60, 5090 Leverkusen 1, Federal Republic of Germany.

Methods

Fifty patients, aged 29 to 66 years (mean 52.1 ± 7.8), with angiographically demonstrated coronary artery disease were studied. All gave signed informed consent. Patients with clinical or radiographic signs of congestive heart failure, large aneurysms, pulmonary diseases, serious arrhythmias or crescendo angina were excluded from the study. All cardioactive drugs were withdrawn at least 72 hours before the trial and sublingual nitroglycerin was not allowed 6 hours before the trial.

The patients were hospitalized in the coronary care unit and a Swan-Ganz catheter was introduced. To prevent the effect of circadian variations,[7] all measurements were obtained at the same hour (in the early afternoon) each day. Hemodynamic measurements were performed at rest. Supine bicycle exercise test was performed and the exercise duration and capacity (product of exercise time in minutes and load in Watts) were determined. The test was symptom-limited, and was discontinued when pulmonary arterial pressure reached 60 mm Hg or more or when ischemic electrocardiographic changes developed in asymptomatic patients.

TABLE I Hemodynamic Effect of Placebo and Various Doses of Isosorbide-5-Mononitrate (IS-5-MN) at Rest

Parameter	Dosage of IS-5-MN (mg) and Placebo	Values	Change (%)	Signif.
HR (beats/min)	Placebo	66.8 ± 9.7 → 64.0 ± 8.2	−4.2	NS
	5			NS
	10	68.8 ± 7.5 → 66.9 ± 5.9	−2.8	NS
	20	67.6 ± 11.2 → 63.9 ± 8.4	−5.5	NS
	50	60.3 ± 6.0 → 66.5 ± 11.0	+9.2	NS
SAP mean (mm Hg)	Placebo	109.5 ± 13.7 → 107.0 ± 13.7	−2.3	NS
	5			NS
	10	112.0 ± 11.5 → 104.5 ± 13.0	−6.6	*
	20	104.7 ± 13.2 → 102.4 ± 14.6	−2.2	*
	50	108 ± 13.6 → 100.9 ± 10.3	−6.6	*
PAP mean (mm Hg)	Placebo	17.8 ± 6.3 → 16.9 ± 5.4	−5.0	NS
	5	16.9 ± 51 → 14.0 ± 4.8	−17.0	†
	10	18.2 ± 5.5 → 15.2 ± 5.0	−16.0	†
	20	15.9 ± 2.9 → 12.1 ± 2.7	−23.9	†
	50	16.8 ± 2.3 → 12.2 ± 2.9	−27.3	‡

* $p \leq 0.05$; † $p \leq 0.01$; ‡ $p \leq 0.001$.
All values are expressed as mean ± standard deviation.
HR = heart rate; NS = not significant; PAP = pulmonary artery pressure; SAP = systemic arterial pressure; Signif. = significance.

TABLE II Hemodynamic Effect of Placebo and Various Doses of Isosorbide-5-Mononitrate (IS-5-MN) During Exercise (50W/3 min)

Parameter	Dosage of IS-5-MN (mg) and Placebo	Values	Change (%)	Signif.
HR (beats/min)	Placebo	101.0 ± 16.2 → 97.6 ± 14.2	−3.3	NS
	5			
	10	103.3 ± 12.2 → 99.1 ± 10.1	−4.0	*
	20	102.9 ± 18.1 → 95.6 ± 13.5	−7.1	*
	50	101.8 ± 11.8 → 97.8 ± 10.0	−3.9	*
SAP mean (mm Hg)	Placebo	124.0 ± 15.7 → 125.0 ± 16.2		NS
	5			NS
	10	128.7 ± 10.5 → 123.1 ± 12.6	−4.3	NS
	20	124.1 ± 19 → 121.3 ± 19.0	−2.3	NS
	50	127.5 ± 13.6 → 122.0 ± 13.2	−4.3	NS
PAP mean (mm Hg)	Placebo	32.6 ± 8.9 → 31.6 ± 7.5	−3.0	NS
	5	38.4 ± 8.5 → 34.6 ± 8.8	−9.9	†
	10	40.6 ± 10.8 → 31.0 ± 10.7	−23.6	†
	20	39.6 ± 9.1 → 26.3 ± 6.4	−33.5	‡
	50	40.3 ± 8.1 → 25.1 ± 6.8	−37.7	‡
Working capacity (W × min)	Placebo	438 ± 80 → 463 ± 86	5.7	NS
	5	297 ± 128 → 319 ± 147	7	NS
	10	315 ± 119 → 418 ± 153	+33	†
	20	293 ± 142 → 524 ± 244	+79	‡
	50	316 ± 149 → 493 ± 151	+56	†
Duration of exercise (sec)	Placebo	398 ± 64 → 428 ± 68	+7.5	NS
	5	294 ± 92 → 310 ± 107	+5	NS
	10	304 ± 93 → 381 ± 118	+25	*
	20	289 ± 106 → 466 ± 197	+61	†
	50	308 ± 105 → 428 ± 95	+39	†

* $p = 0.05$; † $p = 0.01$; ‡ $p = 0.001$.
All values are expressed as mean ± standard deviation.
Abbreviations as in Table I.

When the heart rate and blood pressure returned to baseline, the patients were allowed to rest and received the following treatment: group 1—placebo (8 patients, aged 47 ± 10.7 years); group 2—IS-5-MN, 5 mg orally (10 patients, aged 54.9 ± 6.2 years); group 3—IS-5-MN, 10 mg orally (10 patients, aged 55.8 ± 5.7 years); group 4—IS-5-MN 20 mg orally (11 patients, aged 50.9 ± 8.2 years); and group 5—IS-5-MN, 50 mg orally (11 patients, aged 51.2 ± 6.0 years). The hemodynamic measurements were repeated at 45 minutes after drug administration and the exercise test was also repeated.

Student *t* test was used for evaluation of statistical significance of the results at $p < 0.05$.

Results

All patients completed the study without complications. Results are presented in Tables I and II and Figures 1 to 3.

Heart rate: Heart rate was not altered at rest. During exercise it was not altered with placebo and IS-5-MN, 5 mg, but decreased slightly but significantly with 10, 20 and 50 mg (at comparable workload).

Mean arterial pressure: Placebo and IS-5-MN, 5 mg, did not alter mean arterial pressure. The other doses decreased this parameter slightly but significantly.

Mean pulmonary arterial pressure: Placebo did not alter this parameter at rest or during exercise. All doses of IS-5-MN reduced it in a dose-dependent manner: at rest—5 mg 17%, 10 mg 16%, 20 mg 24%, and 50 mg 27%; during exercise—5 mg 10%, 10 mg 24%, 20 mg 34%, and 50 mg 38%. All changes were significant (Fig. 1).

Work capacity: Placebo and IS-5-MN, 5 mg, did not significantly alter work capacity. After 10, 20 and 50 mg, work capacity significantly increased. After administration of 10 mg, work capacity increased from 315 ± 119 to 418 ± 153 W·min. Seven of the patients in this group increased their work capacity by 75 W·min. Only 3 patients showed only slight increase or no increase at all. After administration of 20 mg, work capacity significantly increased from 293 ± 142 to 524 ± 244 W·min. Only 1 patient did not show an increase in work capacity with this dose. After administration of 50 mg, work capacity significantly increased from 316

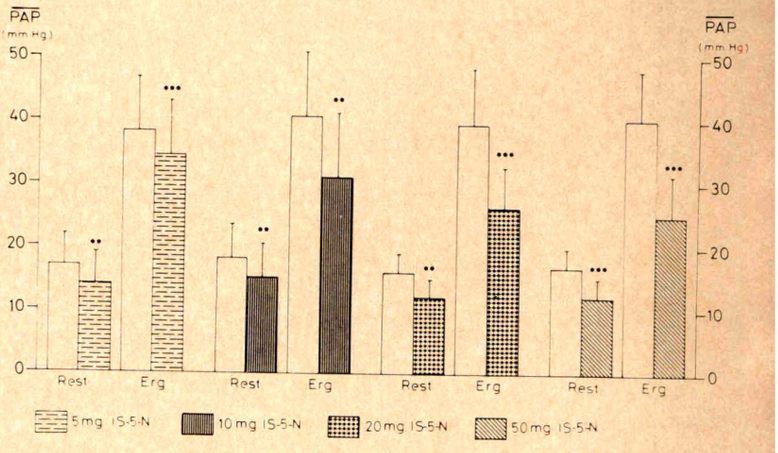

FIGURE 1. Mean pulmonary arterial pressure ($\overline{PAP}$) before (*open bars*) and after various oral doses of isosorbide-5-mononitrate (IS-5-MN). ERG = ergometer. •• = $p \leq 0.01$; ••• = $p \leq 0.001$.

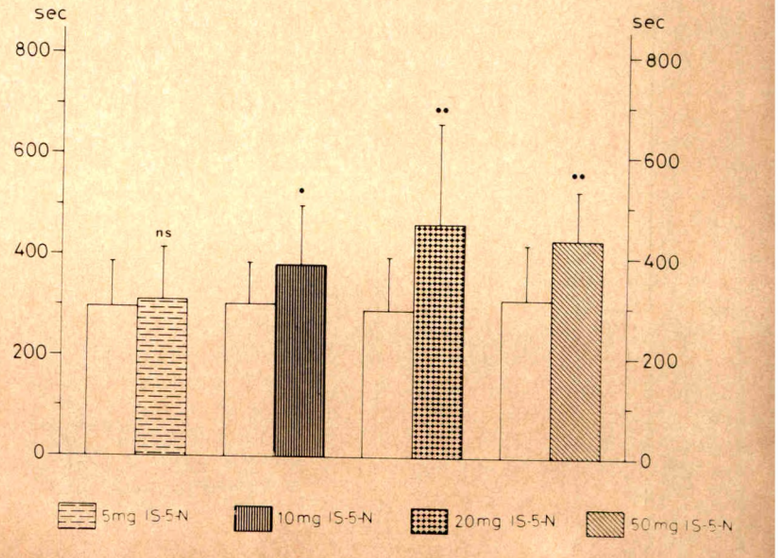

FIGURE 2. Work duration before (*open bars*) and after various oral doses of isosorbide-5-mononitrate (IS-5-MN). • p = 0.05; •• p = 0.01; ns = not significant.

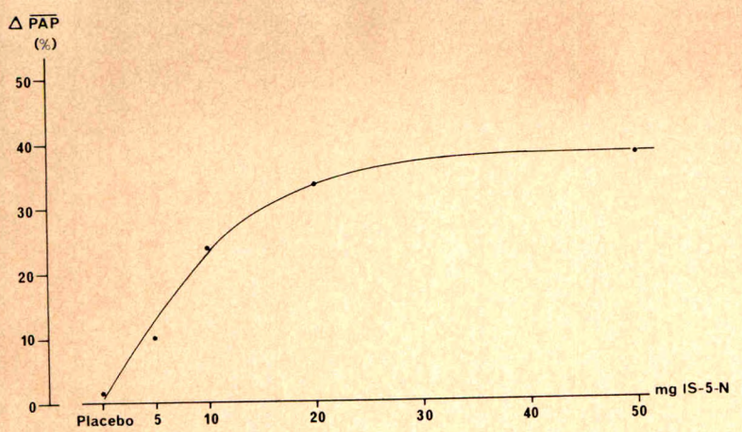

FIGURE 3. Relation of hemodynamic response to dose of isosorbide-5-mononitrate (IS-5-MN). *Ordinates*, percent decrease in mean pulmonary arterial pressure (Δ PAP) during exercise (50 W/3 min). *Abscissa*, dose of IS-5 MN.

± 149 to 493 ± 151 W·min. Only 2 patients had no improvement.

Exercise duration: Placebo and IS-5-MN, 5 mg, did not alter exercise duration. After administration of 10 mg, exercise duration significantly increased from 304 ± 93 to 381 ± 118 seconds (25%); after 20 mg, from 289 ± 106 to 466 ± 197 seconds (61%); and after 50 mg, from 308 ± 105 to 428 ± 95 seconds (39%) (Fig. 2).

Discussion

ISDN has been used for about 20 years for treatment of coronary artery disease, with proved efficacy.[8,9] Determination of dose-effect relations is complicated by the first-pass hepatic metabolism and the variability in absorption (at least with slow-release formulations).[10-12] IS-5-MN, a metabolite of ISDN is effective in coronary artery disease and has the advantages of complete absorption, lack of first-pass hepatic metabolism and pharmacodynamic half-life of 5 hours.[2,4,13-18] Therefore, it is more suitable for prolonged treatment than the parent drug ISDN.

Studies of tolerance development with chronic administration of high doses of nitrates revealed that the dose chosen should be the lowest that is still effective.[19-25] Our study has attempted to determine this dose for IS-5-MN. Systemic arterial pressure is not an adequate parameter to determine dose-response relations for nitrates, as was shown by another study from our group.[26] A better parameter is mean pulmonary arterial pressure, which directly correlates with the preload—the main target for the effect of nitrates—and which can be measured reproducibly.[27] We demonstrated significant and dose-dependent reductions of mean pulmonary arterial pressure with IS-5-MN, at doses of 5 mg or more, the optimal dose being 20 mg (Fig. 3). Single doses of more than 20 mg did not produce any additional benefit. Similar results were obtained in another study by our group, in patients undergoing cardiac catheterization.[26] Also, 5 mg is the initial effective dose and 20 mg the optimal dose for work capacity and duration. Single doses of 50 mg are not more effective than single doses of 20 mg. These results confirm those of Abshagen and Spörl-Radun,[13] demonstrating that an increase in dose to 50 mg produced a slight decrease in therapeutic parameters despite an increase in plasma level.

In conclusion (1) the initial oral dose level of IS-5-MN is 5 mg; (2) the hemodynamic and antianginal (demonstrated by work capacity) effect of a single dose of 10 mg is smaller than that of 20 mg; (3) the optimal effect is achieved with a single dose of 20 mg; and (4) it is preferable not to use doses higher than 20 mg because they do not have an additional therapeutic benefit and may be expected to produce tolerance.[14,28]

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Transdermal Nitroglycerin Patches for Silent Myocardial Ischemia During Antianginal Treatment

ADAM SCHNEEWEISS, MD, and ALON MARMOR, MD

Because silent ischemia is not associated with an increase in heart rate and, being asymptomatic, its treatment requires constant therapeutic plasma levels of the drug used, a transdermal nitroglycerin patch (Deponit®) was selected for treatment of this condition. Eight patients with documented silent ischemia were studied. All patients also had angina on effort treated with calcium antagonists (n = 8) and β blockers (n = 6). They were evaluated by 24-hour ambulatory electrocardiographic monitoring. The transdermal nitroglycerin patch, 20 to 30 mg/24 hours, reduced the number of silent ischemic episodes from 9.25 ± 5.52 to 2.4 ± 2.0 episodes per 24 hours ($p < 0.001$). The maximal ST-segment depression was reduced from 3.1 ± 0.7 to 0.9 ± 0.7 mm ($p < 0.001$). Ventricular premature beats were significantly reduced, by 50%. Symptomatic ischemic episodes were completely suppressed. Thus, transdermal nitroglycerin, in moderate doses, is effective in suppressing silent ischemia in patients with angina pectoris who have silent ischemic episodes despite treatment with other antianginal agents.

(Am J Cardiol 1988;61:36E–38E)

Recently it has been shown that silent myocardial ischemia, not accompanied by chest pain, dyspnea or cardiac arrhythmias occurs more frequently than symptomatic myocardial ischemia.[1,2] Silent myocardial ischemia adversely affects prognosis.[3-5] This justifies treatment to suppress the ischemia, although it has not been shown that such treatment improves prognosis.

Most episodes of silent ischemia are not preceded by an increase of major determinants of myocardial oxygen demand such as heart rate or systemic arterial pressure.[2,6] This finding indicates that β blockers would not be very effective in silent ischemia. Nitrates should be theoretically more useful.

Because the condition is asymptomatic, the most rational approach would be to maintain a constant therapeutic level of the drug in the plasma. Transdermal nitroglycerin patches are optimal for this purpose.[7] This report describes our experience with suppression of silent myocardial ischemia by transdermal nitroglycerin patch (Deponit® 10).

Methods

Eight men, mean age 65.5 ± 12.0 years, were studied. All had chronic stable angina pectoris on effort, with exercise-induced ST-segment depression of ≥2 mm. One had recurrent syncope. One patient had undergone percutaneous transluminal coronary angioplasty and 1 coronary artery bypass surgery >1 year before the study. Results of a 12-lead electrocardiogram were normal in 7 patients and showed flattening of the T wave in 1. All patients were treated with nifedipine, 30 to 60 mg/day, and 6 of them also received propranolol, 80 to 160 mg/day, or atenolol, 100 mg/day. All were also using sublingual nitroglycerin. Ambulatory 24-hour electrocardiographic monitoring was performed using the Marquette system and a computerized ST-segment analyzer. Significant ST-segment depression was defined as the horizontal or downsloping shift of ≥1 mm, occurring for ≥80 ms after the end of the QRS complex, ≥1 minute in duration.

During the first study the patients received their usual antianginal treatment, except for sublingual nitroglycerin. Within 7 days, patients underwent another study, starting 1 hour after application of transdermal nitroglycerin (Deponit 10), 30 mg. After 1 hour, 2 patients had a reduction in dosage to 20 mg—1 because of hypotension and the other because of headache. The patients were instructed to record the time of anginal episodes. The paired *t* test was used to evaluate significance.

From the Geriatric Cardiology Research Foundation and the Cardiology Department, Rebeca Ziv Hospital, Safed, Israel.

Address for reprints: Adam Schneeweiss, MD, 9 Kehilat Sofia Street, 69018 Tel Aviv, Israel.

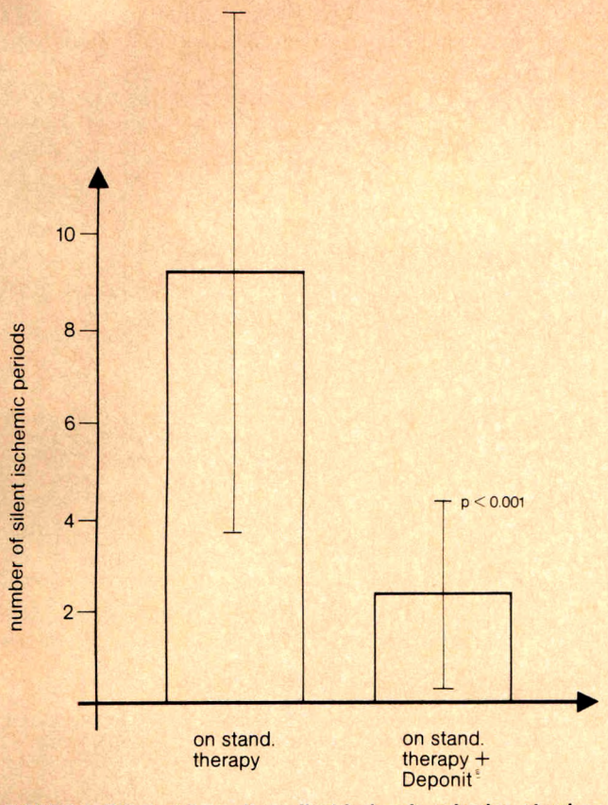

FIGURE 1. Effect of Deponit on silent ischemic episodes. stand. = standing.

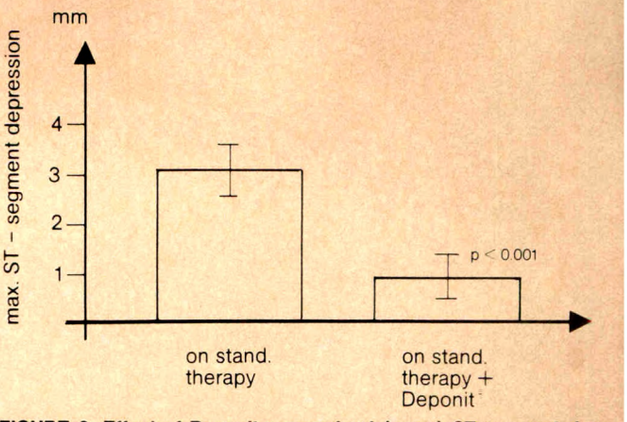

FIGURE 2. Effect of Deponit on maximal (max.) ST-segment depression. stand. = standing.

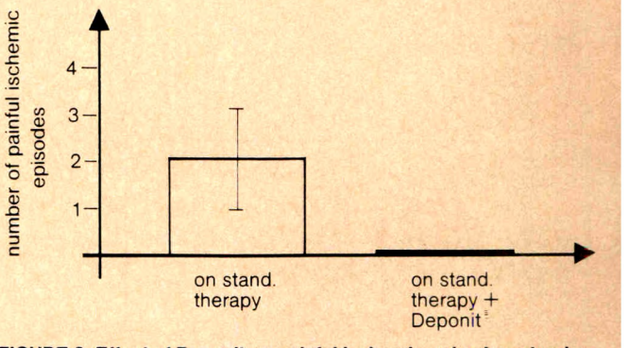

FIGURE 3. Effect of Deponit on painful ischemic episodes. stand. = standing.

Results

All patients completed the study. Treatment with transdermal nitroglycerin resulted in a decrease of silent ischemic episodes from 9.25 ± 5.52 to 2.4 ± 2.0/24 hours ($p < 0.001$) (Fig. 1). The maximal ST-segment depression was reduced from 3.1 ± 0.7 to 0.9 ± 0.7 mm ($p < 0.001$) (Fig. 2). The number of painful ischemic episodes was reduced from 2.1 ± 1.1/day to 0 (Fig. 3). The number of premature ventricular beats was reduced from 243 ± 149 to 121 ± 106/day ($p < 0.05$) (Fig. 4). Runs of ventricular tachycardia were observed in 3 patients without transdermal nitroglycerin and in no patient taking this drug. The frequency of couplets was slightly but nonsignificantly reduced. Adverse effects included hypotension in 1 patient (which responded to reduction in dose) and headache in 3.

Discussion

Our findings indicate that transdermal nitroglycerin (in the form of Deponit) is very effective in suppression of silent myocardial ischemia. The drug was effective in all patients studied. The fact that all patients had silent ischemia while taking various antianginal agents, other than nitrates, was of interest. The addition of transdermal nitroglycerin to this regimen suppressed the silent ischemic episodes.

Several previous studies suggest that nitrates and other antianginal agents are effective in relieving silent ischemia and its consequences. Pepine et al[8] showed that intravenous administration of nitroglycerin reversed asymptomatic episodes of left ventricular dyskinesia attributed to silent ischemia. Glazier et al[9] reported that atenolol is effective in reducing both angina and silent ischemic events in patients with both mixed angina pectoris and silent ischemia. These investigators suggested that in mixed angina, β blockers probably act by reducing the basal metabolic requirements of the heart, thereby making transient reductions in coronary blood flow less likely to reach a critical ischemic level. Perhaps the most important finding of our study is that the patients had silent ischemia despite antianginal therapy (other than nitrates). These episodes were suppressed by nitroglycerin. This may be attributed to the different pathophysiology of painful and silent myocardial ischemia. Selwyn et al[10] studied the myocardial perfusion by positron emission tomography in patients with both painful and silent ischemic episodes. In all their patients, both painful and silent ischemic episodes showed equal decreases in myocardial perfusion. However, angina occurred only when this ischemic insult was enhanced by sufficient increase in myocardial oxygen demand. These findings indicate that impaired perfusion is the primary mechanism of silent ischemia and drug therapy should be directed at improving perfusion rather than reducing myocardial oxygen demand.

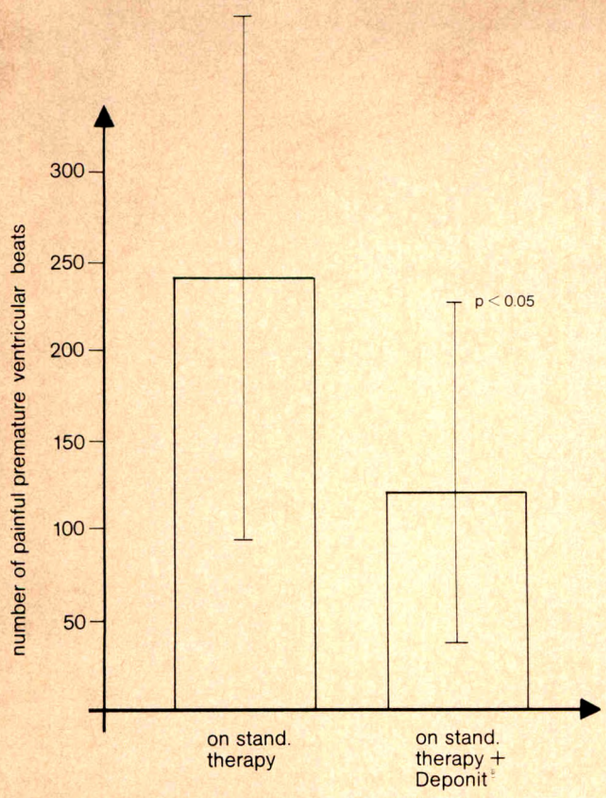

FIGURE 4. Effect of Deponit on premature ventricular beats. stand. = standing.

Another interesting finding was the partial suppression of ventricular premature beats. Myocardial ischemia can be expressed as arrhythmias, and antiischemic agents may thus have an antiarrhythmic effect. Nitrates were shown to possess indirect antiarrhythmic properties in patients with coronary artery disease.[11,12] This activity may be useful in patients with silent ischemia whose episodes are associated with arrhythmias and syncope.

In summary, transdermal nitroglycerin was found very effective in preventing silent myocardial ischemia in patients with angina pectoris who had silent ischemic episodes despite antianginal treatment (other than long-acting nitrates).

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Acute and Sustained Antianginal Effects of Nitroglycerin Patches: Objective Evaluation with Training-Effect-Eliminated Exercise Performance Index

HASAN DOGAR, MD, DENIZ GÜZELSOY, MD, NAZMI GÜLTEKIN, MD, NILGÜN GÜRSES, PhD, and CEM'I DEMIROGLU, MD

A randomized within-patient double-blind acute and sustained study was performed to compare transdermal nitroglycerin (NTG) patches (5 and 10 mg) and matching placebo in 10 patients with chronic stable angina pectoris confirmed on exercise thallium scintigraphy or coronary angiography, or both. Patients performed treadmill tests 2 and 24 hours after application of patches on the first and last days of each of the 3 treatment periods. Effects caused by sequence of treatments and training with serial testing were prominent so the changes in the well-known parameters did not favor either of the active doses over placebo. Quantification of training effects and its subtraction from performance index disclosed that 10 mg of transdermal NTG caused significant increase in performance in both the acute and sustained stages of therapy in comparison to pretreatment performance. This was not observed with 5 mg and placebo treatments.

To our knowledge, this is the first trial to study the efficacy of transdermal NTG with a more objective parameter that permitted elimination of training effects of serial exercise testing.

(Am J Cardiol 1988;61:39E–43E)

Now in its second century of clinical use, nitroglycerin (NTG) is a mainstay of antianginal therapy, and innovative delivery systems have extended the use of it beyond the painful attack.[1] The most recent system works transcutaneously, with daily applied patches releasing NTG at a constant rate over at least 24 hours.[2] NTG plasma levels are dose-dependent, and steady-state plasma levels are reached within 2 hours and maintained for at least 24 hours.[1,3] The present study was designed to assess the efficacy of 2 different doses of a transdermal NTG preparation (Deponit®, Schwarz GmbH) in the prophylaxis of angina pectoris during an acute and sustained study.

Methods

Eight men and 2 women, aged 41 to 64 years (average 52), with chronic stable angina pectoris were studied. The diagnosis of coronary artery disease was confirmed by exercise thallium scintigraphy (n = 9) or arteriographic demonstration of significant luminal narrowing (>70%) of at least 1 major coronary artery (n = 5), or both. Each patient had typical exertional angina and had chest pain during treadmill exercise testing, with a positive test result showing at least 1 mm of horizontal or downsloping ST-segment depression that lasted for at least 80 ms after the J point. No patient had cardiomegaly, congestive heart failure, serious hepatic or renal disease, hypertension, serious conduction disturbances or arrhythmias, diabetes mellitus, anemia, unstable angina or a myocardial infarction within the preceding 3 months. No patient was given digitalis or diuretic or antianginal drugs other than sublingual NTG for the 2 weeks before and during this investigation. All patients gave informed consent for the study.

A randomized within-patient double-blind acute and sustained study, comparing the transdermal NTG patches releasing 5 mg (1 active, 16-cm^2 patch containing 16 mg NTG and a matching placebo patch), 10 mg (2 active patches) and 0 mg (2 placebo patches) over 24 hours, was planned. Patients performed a preliminary symptom-limited treadmill test, which was stopped

From the Institute of Cardiology, University of Istanbul, Istanbul, Turkey.

Address for reprints: Hasan Dogar, MD, Institute of Cardiology, University of Istanbul, Haseki, Istanbul, Turkey.

because of typical angina of moderate severity and horizontal or downsloping ST-segment depression >1 mm and was repeated to judge reproducibility. Of these 2 tests, the one with longer duration of exercise was accepted as the pretreatment test (test I). Patches were mixed after being coded beforehand; thus the sequence of the treatments were taken at random. They were applied to a hairless part of the chest wall every 24 hours for 15 days during each of the 3 treatment periods, which were separated by an interval of 2 or 3 days. During treatments, exercise tests were performed 2 (test II) and 24 (test III) hours after the application of the patches on the first day, and again 2 (test IV) and 24 (test V) hours after the application on the 15th day of each treatment.

Treadmill tests were performed under the same conditions according to the Bruce protocol. Tests II and III were stopped at the end of the same walking time of test I, while tests IV and V were symptom-limited with conventional endpoints.

A 12-lead electrocardiogram was recorded at rest and at every minute during the test and during the 5-minute recovery period. Three leads (V_2, V_4 and V_6) were monitored throughout the test.

Blood pressure was measured with a mercury sphygmomanometer. Heart rate was measured from the electrocardiogram.

The performance index (PI) was calculated from a previously devised formula[4]:

$$PI = t/(PSBP \cdot PHR \cdot 10^{-2})$$

where t = time on treadmill in seconds; PSBP = peak systolic blood pressure; and PHR = peak heart rate.

By eliminating the training effect (TE) of serial exercise testing, corrected PI (PI_c) was obtained, and PI_c was used as an objective parameter in comparing pretreatment performance with performance during each of tests II through V of all the 3 treatments:

$$PI_c = PI - (TE \cdot m)$$

where m = the number of tests a patient had performed between test I and the test in question.

TE is a constant that may be estimated for any trial form:

$$TE = (\Sigma x_p - \Sigma x_i)/n$$

where Σx_p = sum of the PI values calculated in a group of tests at a late control or placebo phase of treatment; Σx_i = sum of the PI values obtained in the pretreatment tests; and n = number of all tests—including those under any treatment—between the pretreatment and the late control tests in all subjects.

In this study, the increase in PI between test II of the placebo phase and test I was taken into account in the calculation of PI_c. One preliminary test was attributed to the familiarity effect and was not included in the evaluation of m.

Student *t* test for paired data was used to assess the statistical significance of differences between pretreatment performance and performance during therapy. Differences were considered significant at $p < 0.05$.

Results

All 10 patients completed the 3 treatments of the study. Two patients had mild headaches for the first 2 days of treatment with active doses. One also had headache with placebo. No other adverse effect was observed.

Analyses of the changes in blood pressure and heart rate at rest, exercise duration, time to development of 1-mm of ST-segment depression, degree of ST-segment depression, peak heart rate, peak systolic blood pressure and double product did not show any significant difference between either of the active doses and placebo in their comparison with pretreatment values. Frequency of anginal attacks and the use of sublingual NTG decreased in 2, 7 and 8 patients receiving treatment with placebo, 5 mg and 10 mg, respectively.

Because effects caused by sequence of treatments and training with serial treadmill exercise testing were prominent, as clearly seen in the mean PI values of the placebo phase, which happened to be the third treatment in more than half of patients, PI_c was devised for the elimination of these effects. Training effect was quantified in reference to the difference of performance between test I and II of the placebo phase, which yielded an optimal constant (0.08 per test), with a much lower value than that estimated from test V of the placebo phase (0.13 per test).

PI in test I and the PI, PI_c and m values in all the treatments in 10 patients are given in Table I. Mean PI (± standard deviation) and mean PI_c (± standard deviation) are shown in Table II. Three of 4 mean PI values obtained with placebo were higher than those with the active doses. In terms of PI_c, however, a significant increase in performance was found at the second hour of application of both the active doses on the first day (acute study period) compared with pretreatment and placebo values. At the 24th hour of acute therapy and at the second and 24th hours on the 15th day (sustained therapy), mean PI_c values with 10-mg patches were significantly higher than mean PI during pretreatment, although not significantly different from those of the placebo and 5-mg treatments.

Although some mean PI_c values with placebo and 5-mg treatments were higher than that calculated in test II of the 10-mg treatment, they were not significantly different from the pretreatment PI, because the statistical analysis was based on paired data, which compared the variations within each patient.

Discussion

Since its introduction in 1981 as a new approach to prolonging nitrate action, transdermal NTG delivery system has gained wide acceptance in the clinical community. Recently, however, questions have arisen regarding the efficacy of transdermal patches in the prevention of anginal attacks in coronary artery disease.[5-7] Nevertheless, many factors (e.g., protocol and design, the subjects chosen, and even the physicians conducting the clinical trials) are challenged.[8] In fact, the Food and Drug Administration developed criteria

TABLE I Sequence of Treatments (TS), Performance Index (PI), Corrected PI (PI_c) and Number of Tests Performed Before Each Test (m) in 10 Patients

Pt	TS (mg)		Test I	Test II			Test III			Test IV			Test V		
				0	5	10	0	5	10	0	5	10	0	5	10
YO	5-10-0	PI	2.80	3.20	2.50	2.98	3.20	3.08	3.70	2.45	2.31	3.20	3.14	2.74	3.15
		m		9	1	5	10	2	6	11	3	7	12	4	8
		PI_c		2.48	2.42	2.58	2.40	2.92	3.22	1.57	2.07	2.64	2.18	2.42	2.51
ND	5-10-0	PI	2.24	3.21	3.19	3.67	3.41	4.16	4.24	2.79	2.62	2.69	2.92	3.78	4.17
		m		9	1	5	10	2	6	11	3	7	12	4	8
		PI_c		2.49	3.11	3.27	2.61	4.00	3.76	1.91	2.38	2.13	1.96	3.46	3.53
RY	10-0-5	PI	2.42	2.92	3.75	3.55	3.41	3.52	2.99	3.02	3.53	3.63	5.18	4.44	3.13
		m		5	9	1	6	10	2	7	11	3	8	12	4
		PI_c		2.52	3.03	3.47	2.93	2.72	2.83	2.46	2.65	3.39	4.54	3.48	2.81
SM	10-5-0	PI	2.81	3.19	3.25	3.16	3.25	3.38	3.53	3.65	3.29	3.31	3.31	2.54	4.41
		m		9	5	1	10	6	2	11	7	3	12	8	4
		PI_c		2.47	2.85	3.08	2.45	2.90	3.37	2.77	2.73	3.07	2.35	1.90	4.09
MZ	5-10-0	PI	1.96	2.80	2.44	2.50	3.93	2.04	3.02	3.38	2.26	3.09	3.44	3.02	3.37
		m		9	1	5	10	2	6	11	3	7	12	4	8
		PI_c		2.08	2.36	2.10	3.13	1.88	2.54	2.50	2.02	2.53	2.48	2.70	2.73
HG	10-0-5	PI	1.19	1.35	2.15	1.59	1.29	2.03	1.40	1.43	2.52	1.81	1.56	3.07	1.56
		m		5	9	1	6	10	2	7	11	3	8	12	4
		PI_c		0.95	1.43	1.51	0.81	1.23	1.24	0.87	1.64	1.57	0.92	2.11	1.24
AT	5-10-0	PI	1.44	1.84	1.56	1.73	2.57	2.07	2.47	4.76	1.92	2.60	3.96	1.93	2.85
		m		9	1	5	10	2	6	11	3	7	12	4	8
		PI_c		1.12	1.48	1.33	1.77	1.91	1.99	3.88	1.68	2.04	3.00	1.61	2.71
SD	5-10-0	PI	1.54	2.52	1.67	2.44	2.85	1.75	2.27	2.58	3.28	3.49	2.49	2.76	2.85
		m		9	1	5	10	2	6	11	3	7	12	4	8
		PI_c		1.80	1.59	2.04	2.05	1.59	1.79	1.70	3.04	2.93	1.53	2.44	2.21
HY	10-0-5	PI	0.91	1.51	1.88	1.50	1.54	1.41	1.55	3.18	2.00	1.99	2.52	1.94	1.91
		m		5	9	1	6	10	2	7	11	3	8	12	4
		PI_c		1.11	1.16	1.42	1.06	0.61	1.39	2.52	1.12	1.75	1.88	0.98	1.59
HD	0-5-10	PI	1.99	2.20	2.96	2.67	2.57	2.80	3.60	3.01	4.20	3.72	3.94	3.83	3.05
		m		1	5	9	2	6	10	3	7	11	4	8	12
		PI_c		2.12	2.56	1.95	2.41	2.32	2.80	2.77	3.67	2.84	3.62	3.19	2.09

TABLE II Mean Performance Index (PI ± SD) and Mean Corrected PI (PI_c ± SD) in Pretreatment Tests and in Tests During Three Treatments in 10 Patients

Test No.		Pretreatment	Treatment 0	Treatment 5	Treatment 10
I	PI	1.93 ± 0.65			
II	PI		2.47 ± 0.71	2.54 ± 0.75	2.58 ± 0.78
	PI_c		1.91 ± 0.63	2.20 ± 0.72*†	2.28 ± 0.79*‡
III	PI		2.80 ± 0.84	2.62 ± 0.90	2.88 ± 0.94
	PI_c		2.16 ± 0.76	2.21 ± 0.98	2.49 ± 0.86**
IV	PI		3.03 ± 0.86	2.79 ± 0.75	2.95 ± 0.66
	PI_c		2.30 ± 0.83	2.30 ± 0.75	2.49 ± 0.60**
V	PI		3.25 ± 0.99	3.01 ± 0.82	3.05 ± 0.87
	PI_c		2.45 ± 1.05	2.43 ± 0.82	2.50 ± 0.85**

* $p < 0.05$ vs test I; ** $p < 0.01$ vs test I; † $p < 0.05$ vs placebo; ‡ $p < 0.01$ vs placebo.
SD = standard deviation.

for assessing the effectiveness of antianginal agents by comparing pretreatment performance with performance during therapy at symptom-limited treadmill exercise testing.[8,9]

The accurate evaluation of clinical efficacy of an antianginal drug is fraught with difficulties when subjective parameters, such as changes in incidence of anginal attacks and NTG consumption,[10] and objective indexes of effort-induced myocardial ischemia, such as ST-segment depression, workload, time on treadmill, heart rate and blood pressure responses,[4] are used. Many studies evaluating the efficacy of transdermal NTG using these parameters have been performed, and the results and reasons for inconsistencies are reviewed elsewhere.[2,11,12] Perhaps the most difficult question remains: What measure of efficacy is clinically most relevant?[2] The number of patients, on the other hand, was exceedingly small in all of these acute (average 10 patients) or sustained (14.6 patients) studies,[2] and a unique multicenter large trial with NTG patches is still in progress in conjunction with the Food and Drug Administration, academic community and industry.

With respect to design, this trial resembles most of the trials including short- and long-term therapy. Every effort was made to standardize the conditions of the exercise tests. In terms of the aforementioned parameters, however, statistical significance was not achieved against placebo, and numerical results were not given, although they appeared to have clinical significance against pretreatment values. It has been recently demonstrated that placebo, in a single- or double-blind protocol, does not affect the objective indexes of effort-induced myocardial ischemia[10]; however, the reverse may be true in such a trial as this, in which every patient underwent at least 14 exercise tests in less than 2 months. Then, the improvement in the indexes during the placebo therapy should have been due to the placebo effect and to the familiarity and training effects with repeated exercise testing, the latter not being dealt with or sufficiently detailed in most published studies.[2]

This assumption led us to the tentative quantification of TE by using the PI that has recently been proposed by Miller and Grais.[4] The reasons for choosing this index were: (1) It included, in itself, 3 indexes as components of performance; and (2) as one would expect, it reflects the effects of physical training very well.[4] Also, because of its latter property, the analysis of differences in raw PI values obtained during each of the 3 treatments did not result in statistical significance. When we assumed that a factor that can be subtracted from all PI values obtained in all the tests during treatments would eliminate TE, an optimal constant was estimated to represent TE for every test in this study group. Surprisingly, the analysis of differences in terms of PI_c, which was obtained by the reduction of PI as defined in the Methods section, resulted in statistical significance proving the efficacy of 5 and 10 mg of transdermal NTG 2 hours after application in acute therapy compared with placebo and pretreatment control. It also demonstrated the efficacy of 10 mg of transdermal NTG 24 hours after application in acute therapy and 2 and 24 hours after the last application in sustained therapy compared with pretreatment performance; however, PI_c of placebo and 5 mg of transdermal NTG at these instances were not statistically significant from pretreatment performance.

This outcome may explain the inconsistencies within those "negative" trials[5,13] of transdermal NTG in which results appeared to have clinical significance (quantitative increase), yet statistical significance was not achieved.

Even after the subtraction of TE, average performance with placebo and 5 mg showed improvement, although statistically not significant. In the case of the placebo treatment, this may be due to the prominent placebo effect in some patients and supports the idea that new antianginal drugs should be compared with drugs of established antianginal efficacy, rather than with placebo periods.[5] With 5-mg treatment, it might be due to the marked individual variability in NTG sensitivity (i.e., some nitrate-responsive patients may truly derive a real benefit from low-dose transdermal NTG).[6]

In conclusion, this study, representing the first to exclude the training effects in exercise testing, demonstrates that transdermal NTG patches releasing 10 mg are effective in improving the exertional performance in a group of patients with coronary artery disease for a period of 15 days.

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Efficacy of a New Transdermal Nitroglycerin Patch (Deponit 10) for Stable Angina Pectoris

RAFFAELE GRECO, MD, DORIANA D'ALTERIO, MD, MARIO SCHIATTARELLA, MD, ANGELO BOCCIA, MD, LUIGI GRECO, MD, and FEDERICO MARSICO, MD

In this double-blind randomized placebo-controlled crossover study, the antianginal and anti-ischemic effect of a new transdermal system, releasing 10 mg of nitroglycerin (NTG) over 24 hours, was assessed in 19 outpatients with stable exercise-induced angina pectoris. The trial consisted of a 3-day washout: a 1-week period with verum or placebo patch followed by a second 1-week period with the other patch. During the study only sublingual NTG was allowed, and its consumption and the number of attacks recorded. Treadmill exercise tests were performed at the end of washout before patch application (baseline test) and 3 and 24 hours, respectively, after each period of 7 days of application of 1 patch daily.

Systolic blood pressure and heart rate did not vary significantly at rest in the 17 patients who completed the trial. Angina was reduced 31.3% and NTG consumption 34.3% ($p < 0.01$) during the week with Deponit® 10 as compared with placebo. Exercise duration increased 29 and 16.1% ($p < 0.001$ and $p < 0.1$, respectively) at 3 and 24 hours with a verum patch as compared with placebo. ST-segment depression at comparable loads decreased 69 and 40.5% ($p < 0.01$) at 3 and 24 hours, respectively, after application of Deponit. Onset of angina was delayed and maximal heart rate–blood pressure product significantly increased at 3 and 24 hours of treatment. It is concluded that Deponit 10 patch is effective in reducing anginal attacks and in increasing exercise capacity up to 24 hours after application.

(Am J Cardiol 1988;61:44E–51E)

The efficacy of nitroglycerin (NTG) for rapid relief of angina pectoris has long been known, but its role for the chronic management of ischemic heart disease has been limited by short duration of action, when administered sublingually and by extensive enterohepatic clearance when administered orally.

An alternative approach to prolong the action and to increase plasma levels of NTG has been transdermal delivery of NTG by ointment that is absorbed through the skin and, bypassing the gastrointestinal tract, avoids rapid first-pass metabolism within the liver.[1,2] The disadvantages of this method, consisting of several rather inconvenient applications and of variable plasma levels, have prompted research for other transdermal delivery systems in the form of discs or patches.[3]

From the Cattedra di Cardiologia, I°Policlinico, Università di Napoli e Divisione di Cardiologia, Ospedale Monaldi, Napoli, Italy.

Address for reprints: Raffaele Greco, MD, Viale Winspeare 19 (Vomero), Napoli 80127, Italy.

Despite wide acceptance of these new devices[4] for treatment of both angina[5–8] and heart failure,[9–12] much controversy remains concerning efficacy, dosage requirements and duration of action of NTG.[13–27] Recent editorials have pointed out that, while a great number of short- and long-term studies have been performed, there is a need for large and well-controlled studies before firm conclusions can be drawn.[4,13,17]

In this study, which is a double-blind randomized placebo-controlled crossover trial, the antianginal efficacy of a new NTG delivery system (Deponit® 10, Schwarz GmbH) designed to release 10 mg of NTG within 24 hours, has been evaluated in patients with stable angina pectoris.

This new device has been extensively investigated by several workers[28–30] both in vitro and in vivo: plasma concentration reaches maximal levels 2 to 3 hours from application and a plateau is then maintained up to 24 hours.[28] The adhesive film of Deponit 10 has a surface area of 32 cm^2 and contains 32 mg of glyceryl trinitrate that is released at an average absorption rate of 10 mg/24 hours.

Methods

Nineteen men with stable exercise-induced angina, which was relieved by sublingual NTG, entered the study after giving written informed consent. Their ages ranged from 39 to 69 years (mean 53.0), body weight ranged from 62 to 84 kg (mean 71.0) and height ranged from 163 to 180 cm (mean 170.0). Each patient had 2 to 6 attacks of angina per week, relieved by rest or sublingual NTG, with unchanged pattern within 1 month preceding the study. Fourteen patients had had a myocardial infarction more than 3 months previously and a coronary angiogram showed multivessel disease in 10. Ischemic heart disease had been assessed by history and positive treadmill test results in all patients. All patients had been receiving long-term treatment with nitrates and were familiar with the treadmill technique for exercise testing at the time of enrollment. Five patients had normal results and 14 had abnormal results (presence of pathologic Q waves related to previous infarction) on electrocardiography.

Exclusion criteria were angina at rest or a changing pattern in the last month, recent myocardial infarction within 3 months, heart failure, left ventricular aneurism, large anterior infarction hindering evaluation of ST-segment during the test, atrioventricular or intraventricular conduction disturbances, left ventricular hypertrophy, ST-segment depression at rest, valvular heart disease, cardiomyopathy, complex arrhythmias at rest, serious disease of other organs or systems, need for digitalis, diuretics, calcium-antagonists, β blockers or antiarrhythmic drugs.

All patients who consented to the study were allowed to take NTG only and were requested to keep a diary of all anginal attacks and consumption of NTG tablets. If angina worsened at any time the patient was withdrawn from the study and was assigned to a more complex therapy.

Trial procedure: The study covers a period of 18 days (Fig. 1) and was a placebo controlled trial in a double-blind and randomized crossover design. After a 3-day washout period during which a placebo patch was applied every morning to a hairless part of the thorax and kept in place for 24 hours, on the fourth day each patient underwent a baseline treadmill test after heart rate and blood pressure were recorded in the supine and standing positions. After this time 0 test, medication-1-patch, which could be verum or placebo according to the randomization procedure, was applied. The same medication was applied at the same time for 7 days. On the seventh day (day 10) the patients performed a treadmill test 3 hours after the last application of medication-1-patch, after checking heart rate and blood pressure in the supine and standing positions. On the following day (day 2 from the start of the study), exactly 24 hours after the last application, after obtaining baseline data, another treadmill test was performed.

Immediately after recovery from this test the first medication-2-patch (crossover) was applied and so on for the next 6 days. On days 17 and 18, a treadmill test was performed at 3 and 24 hours after the last application of medication-2-patch, respectively. Heart rate and blood pressure at rest in the supine and upright positions were recorded before exercise testing on days 1, 4, 10, 11, 17 and 18 (Table I). Symptoms, adverse effects, compliance and adhesiveness of patches were checked ahead of each session.

Experimental procedure: Nineteen men, younger than age 70 years, with stable angina were admitted to the study. After a 3-day washout (9 patients were taking calcium antagonists, none were taking β blockers and 19 were taking nitrates). On the fourth day of the trial all patients underwent a baseline treadmill test according to the Bruce protocol. Exercise testing was performed in the morning in the fasting state.

Seventeen patients completed the trial undergoing a total of 5 tests (2 patients had to be withdrawn prema-

TABLE I Variations in Systolic Blood Pressure and Heart Rate at Rest in Supine and Standing Positions (n = 17)

Variable	Baseline	Deponit (3 hours)	Deponit (24 hours)	Placebo 1 (3 hours)	Placebo 1 (24 hours)
BP supine (mm Hg)	141 ± 14	140 ± 15	136 ± 12	136 ± 14	137 ± 12
BP standing	140 ± 18	137 ± 15	137 ± 13	136 ± 13	137 ± 13
HR supine beats/min	69 ± 6	70 ± 4	69 ± 5	68 ± 4	70 ± 5
HR standing (beats/min)	74 ± 7	74 ± 5	73 ± 7	72 ± 4	73 ± 4

Differences are not statistically significant.
BP = blood pressure; HR = heart rate.

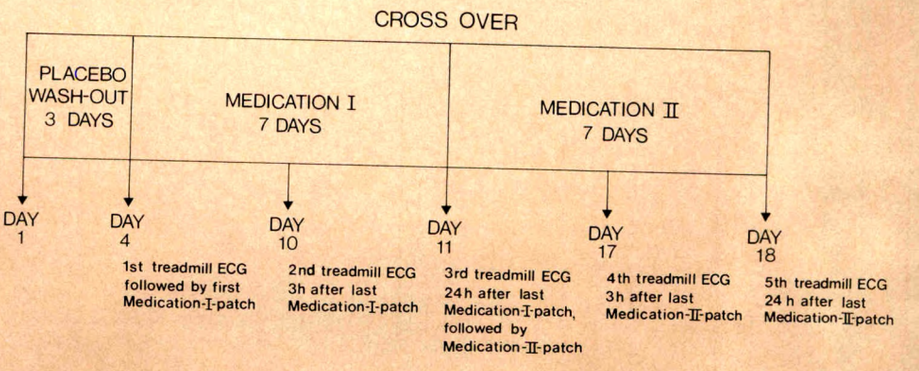


FIGURE 1. Study design: placebo-controlled double-blind randomized crossover study. ECG = electrocardiogram.

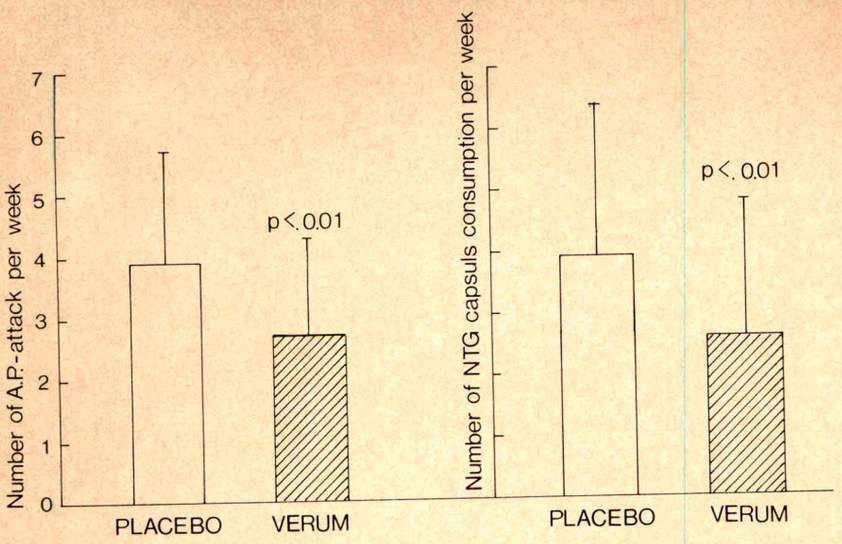


FIGURE 2. Changes in number of attacks of angina pectoris (A.P.) and nitroglycerin capsule consumption per week taking Deponit 10 compared with placebo.

TABLE II Exercise Duration in Each Patient Taking Different Medications and at Baseline (seconds)

n	Baseline	Placebo (3 hours)	Deponit (3 hours)	Δ	Placebo (24 hours)	Deponit (24 hours)	Δ
1	340	320	450	+130	330	360	+30
2	450	360	420	+ 60	360	360	0
3	330	310	360	+ 50	300	360	+60
4	480	360	480	+120	330	420	+90
5	340	310	420	+110	330	360	+30
6	640	700	600	−100	540	600	+60
7	270	390	510	+120	360	480	+120
8	330	360	450	+ 90	360	420	+60
9	240	300	360	+ 60	300	300	0
10	250	300	300	0	330	300	−30
11	360	420	420	0	360	540	+180
12	600	540	660	+120	540	690	+150
13	420	510	600	+ 90	540	560	+20
14	300	300	660	+360	330	360	+30
15	360	340	420	+ 80	300	360	+60
16	300	360	520	+160	420	480	+60
17	240	330	360	+ 30	270	330	+60

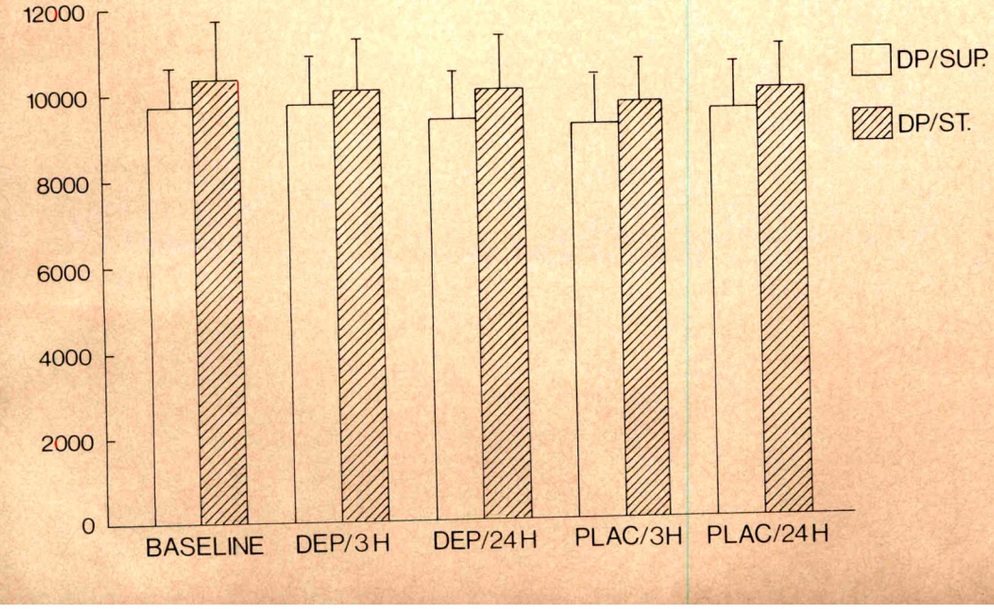


FIGURE 3. Changes in double product (DP) at rest. DEP = Deponit; PLAC = placebo; ST. = standing; SUP. = supine.

turely for worsening of angina). Ten patients received the verum patch initially and then crossed over to the placebo patch; 9 received the placebo first. One patient from each arm of the trial was withdrawn prematurely before completing the trial.

Endpoints of exercise testing were exhaustion, angina of moderate severity, ST-segment depression ≥2 mm in any lead, dyspnea, failure of systolic blood pressure to increase within 2 stages, complex ventricular arrhythmias, systolic blood pressure >200 mm Hg or diastolic blood pressure >100 mm Hg, and symptoms or signs related to cerebral hypoxia.

One or more of the following criteria were used for a positive result: typical anginal pain of moderate severity, horizontal or downsloping ST-segment depression ≥1.5 mm, 0.08 second from the J point, and a decrease in blood pressure of 10 mm Hg or more.

A 9-lead electrocardiogram was recorded at rest, at the end of each treadmill stage and at every minute during a 10-minute recovery period. Three leads at a time were monitored continuously on a memory oscilloscope (D_1, D_2, D_3, aVR, aVL, aVF, V_2, V_4 and V_6). Blood pressure was recorded every minute by sphygmomanometer by the same operator. Heart rate was measured by electrocardiography. The laboratory temperature was between 23°C and 26°C and all patients were familiar with the treadmill system, having undergone at least another treadmill test previously.

The main criteria for evaluating efficacy of the drug in the trial were the number of anginal attacks and consumption of NTG capsules per week, exercise duration, time to onset of ST-segment depression, and time to onset of moderate angina.

Statistical analysis: The randomization process distributed patients in such a fashion that 10 patients initially received the drug and 9 the placebo in the first arm of the crossover. Because 1 patient from each group withdrew at the beginning of the trial, 9 patients receiving the drug first and 8 patients receiving the placebo initially completed the trial. Analysis of variance, Student *t* test and chi-square test were used depending on the variables considered to evaluate the differences between the 2 treatments.

Results

The trial was interrupted prematurely by 2 patients because of worsening of angina; subsequent outcome was benign in both cases. One patient had completed the baseline test and it was during the placebo week; the other patient had performed the baseline and the 3-hour test after receiving Deponit 10 at the end of the first week of trial.

Antianginal effect: In 17 patients (89.4%) who completed the study, a significant reduction of angina and NTG consumption was observed during treatment with Deponit 10 compared with placebo: Angina was reduced from 3.9 ± 1.7 attacks per week with placebo to 2.7 ± 1.6 (−31.3%) ($p < 0.01$) with treatment, and NTG capsule consumption diminished from 3.9 ± 2.4 to 2.6 ± 2.2 (−34.3%) ($p < 0.01$) (Fig. 2).

Effect at rest: Heart rate and systolic blood pressure both in the supine and standing positions did not show significant variation during treatment compared with placebo (Table I). Double product at rest (Fig. 3) did not change significantly as well and a small difference was observed between supine and standing positions (difference not significant).

Exercise testing: Table II lists exercise duration in each patient who completed the trial taking different medication and at baseline. Fourteen patients improved their endurance capacity at 3 hours taking Deponit 10 compared with placebo; one patient's condition worsened and 2 had no improvement. At 24 hours, a slight increase in duration was still present in 14 patients, no difference with placebo could be demonstrated in 2 and the condition of 1 patient was worse than with placebo.

Table III summarizes exercise duration, ST-segment depression at maximal and comparable loads, maximal pressure-rate product and change in reason for terminating the test. Because exercise duration coincided with time to onset of moderate angina in all patients but 1, only exercise duration is listed in the table. Exercise duration increased 29% ($p < 0.001$) and 16.1% at 3 and 24 hours, respectively, during treatment compared with baseline, whereas the increment was 26.2% ($p < 0.001$) and 15.3% ($p < 0.01$) compared with placebo (Fig. 4).

ST-segment depression at maximal load, i.e., end of exercise, was significantly different at baseline and with placebo, whereas ST depression at comparable exercise levels (Fig. 5) showed a significant difference both at baseline and with placebo. Three hours after administration of Deponit 10, a 66.6% reduction of ST-segment depression ($p < 0.01$) was demonstrated compared with baseline values and a 60% reduction compared with placebo after 3 hours ($p < 0.01$). At 24 hours a 41% reduction at baseline ($p < 0.01$) and a 30% reduction with placebo ($p < 0.05$) could be seen (Table III). Double product at maximal exercise did not significantly increase compared with placebo at 3 and 24 hours (6.7 and 4.1%, respectively), whereas a slight significance ($p < 0.05$) could be demonstrated at baseline (+8.1 and 7.8% at 3 and 24 hours, respectively, with Deponit) (Table III).

At baseline, all patients stopped exercising because of moderate angina, whereas 16 patients had angina as the endpoint during all subsequent tests. Only 1 patient became asymptomatic during all tests after the baseline. No patient had to terminate the test because of arrhythmias, heart failure or a decrease in blood pressure.

Time to ST-segment depression of 1 mm increased significantly compared with placebo only 3 hours after administration of Deponit (Fig. 6). Time for ST displacement to return to baseline decreased only slightly but not significantly during the 3- and 24-hour tests with Deponit compared with placebo and baseline (Fig. 7).

Adverse effects and adhesiveness of patches: The adhesiveness of patches was absolutely satisfactory because no detachment was noticed both by the patients and at control visits.

No accidents or complications occurred during the trial. Three patients complained of severe headache during the first days of treatment with verum patch

TABLE III Changes in Exercise Duration, ST-Segment Depression, Maximal Double Product and Causes for Termination of Exercise (n = 17)

Variable	Baseline	Deponit (3 hours)	Deponit (24 hours)	Placebo (3 hours)	Placebo (24 hours)
Duration (sec.)	369 ± 116	476 ± 118	428 ± 113	377 ± 90	371 ± 87
ST at max. load (mm)	1.5 ± 0.6	1.4 ± 0.6	1.4 ± 0.7	1.4 ± 0.7	1.4 ± 0.7
ST at comp. load	1.2 ± 0.7	0.4 ± 0.6†	0.7 ± 0.8*	1.0 ± 0.7	1.0 ± 0.8
Max DP ($\times 10^2$)	234 ± 29	253 ± 29*	252 ± 34*	237 ± 24	242 ± 15
Angina	17	16	16	16	16
Tiredness	0	1	1	1	1

* $p < 0.05$; † $p < 0.01$.
DP = double product; comp. = comparable; max. = maximal.

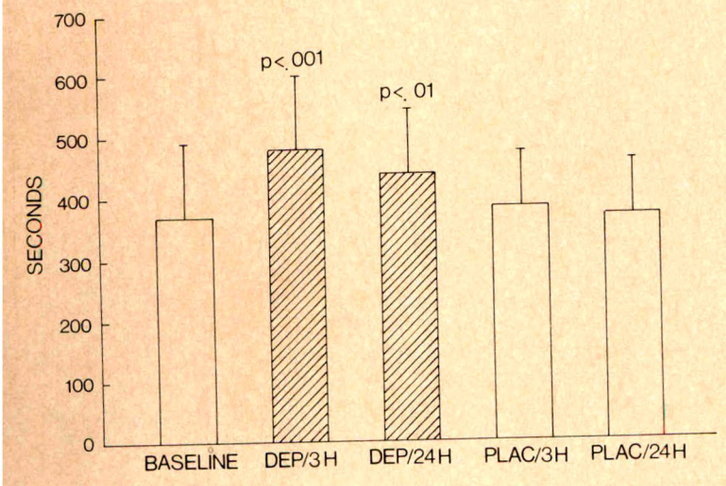


FIGURE 4. Duration of exercise time with different medications (comparison with placebo [PLAC] is indicated). DEP = Deponit.

compared with 1 patient during treatment with placebo. A slight skin erythema or local irritation was observed in 7 patients using the verum patch (36.8%) and in 1 patient taking placebo (5.2%).

Discussion

In this double-blind placebo-controlled crossover trial, a significant antianginal effect of a new transdermal NTG patch (Deponit 10) has been seen by more than a 30% reduction of anginal episodes and NTG consumption during the week of treatment compared with the week of placebo therapy. Despite the limitation that NTG plasma levels were not measured, the particular design of this study should not consider these results too subjectively and they should be discounted on that basis. This finding is in agreement with other investigators who reported reduction of anginal attacks during 2 to 3 weeks of treatment with transdermal NTG delivery systems.[3,5,22-25]

Moreover, objective means of quantifying the anti-ischemic effect of Deponit 10 is provided by a significant improvement of exercise endurance and delay of onset of angina during exercise both at 3 and 24 hours after patch application and by significant reduction of ST-segment depression at comparable exercise level. Time for regression of ST displacement was significant only at the 3-hour test, and double pressure-rate product presented only minimal changes at maximal exercise duration. To summarize, our data show an increase in exercise capacity with Deponit 10 and a significant anti-ischemic effect, which is more evident at 3 hours but still evident at 24 hours from the last application.

These observations are in agreement with most investigators who have demonstrated efficacy at 3 to 8 hours with transdermal NTG systems,[4,8,14,18,31] but antianginal and anti-ischemic efficacy at 24 hours is more difficult to demonstrate.[10,17,19,20,31] However, even among some of the negative trials, parameters other than total exercise duration, such as development of angina during exercise, time to ST-segment displacement of 1 mm and episodes of ST-segment displacement at Holter monitoring show significant improvement up to 24 hours.[14,15] On the basis of serial multigated radionuclide ventriculographic studies, hemodynamic improvement over 24 hours has recently been demonstrated in patients with angina pectoris.[10] In other studies, results that show improvement of

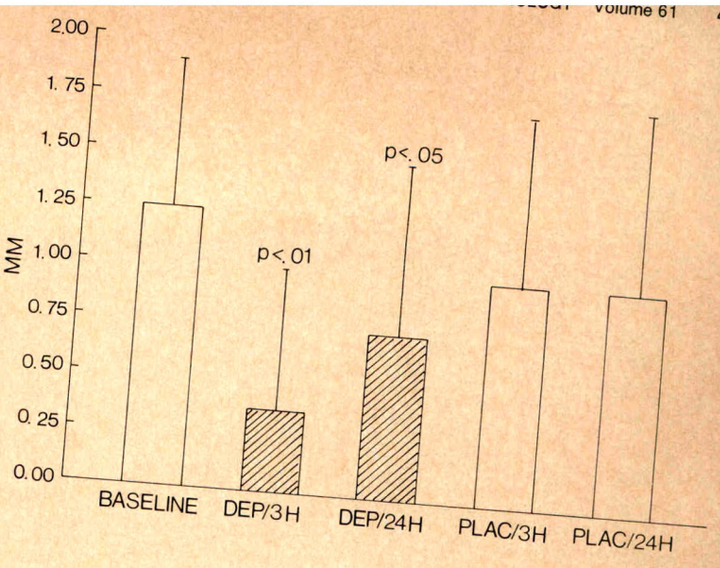
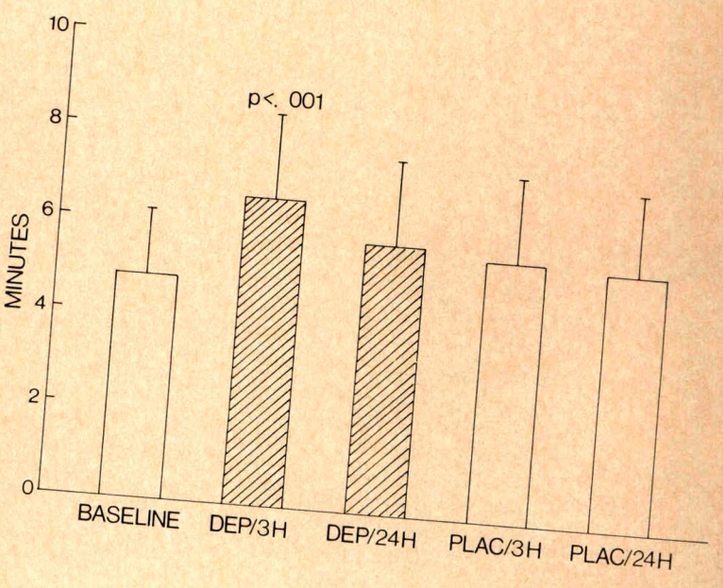
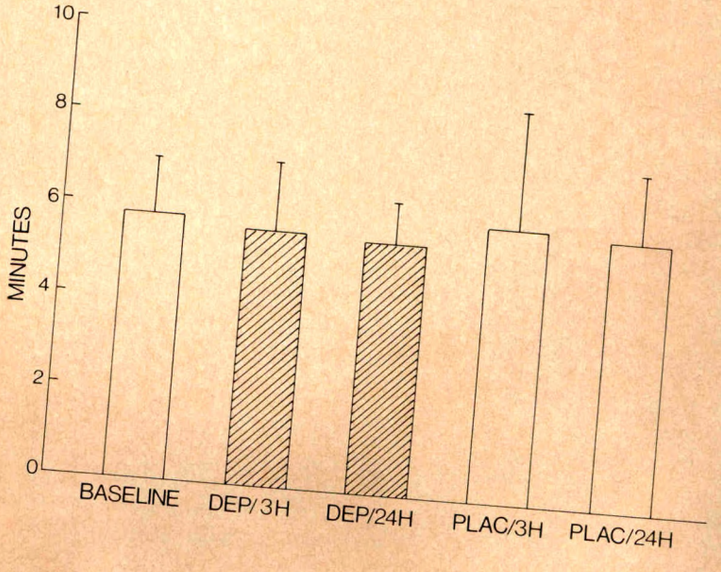


FIGURE 5. ST-segment depression under comparable load (difference with placebo (PLAC) is significant). DEP = Deponit.



RE 6. Time of ST-segment depression of 1 mm g exercise. DEP = Deponit; PLAC = placebo.



Time of return of ST-segment depression to e (0 mm) in recovery stage. DEP = De- = placebo.

some clinical significance fail to reach statistical significance probably because of a small number of patients in the trial.[7] Our data demonstrate a slight but significant effect present at 24 hours, which is in agreement with studies on other transdermal preparations.[3,5,10,21-23]

This study also demonstrated a lack of significant changes in heart rate and blood pressure at rest during treatment. This may have occurred because all of our patients had been receiving long-term therapy with nitrates when they entered the trial, which may have attenuated the decrease in systolic pressure and increase in heart rate as should be expected.[27,32,33] On the other hand, the relevance of this hemodynamic tolerance to the antianginal effect of transdermal NTG is the object of harsh debate.[34] Several investigators[7,8,15,16,18] have shown that increasing doses are required after exposure to oral or transdermal nitrate therapy, but many studies show a sustained effect despite treatment with transdermal NTG up to a period of 3 weeks.[5,14,18,22,24] The particular design of our trial, with a double-blind randomized sequence of placebo and verum patch, should have protected results from tolerance or "training" effects.

Finally, interpatient variability has been noted: Some patients presented a marked antianginal and anti-ischemic effect, some a slight effect, and others did not improve or did worse at exercise despite weak improvement of angina during the week of treatment with the verum patch. This observation is consistent with other studies in patients with angina or heart failure[4,7-11,28] and this range of responses may be explained on the basis of different absorption of transdermal NTG, resistance to NTG, cross tolerance with other nitrates, different response to the same dose of NTG in the individual patient, rapid tolerance developing in some patients, or different mechanism of action for each patient as pointed out by Scardi et al.[23] Ischemia may, in fact, be relieved by NTG from both a decrease in myocardial requirements for oxygen and an increase in oxygen supply. Accordingly, reduction of systolic arterial pressure or a decrease of venous pressure may occur as well as an increase of blood flow through dilatation of stenotic vessels or collaterals. In an individual patient, any 1 or all of these hemodynamic changes may take place. Patients whose conditions improve while taking low doses of NTG, according to Brown et al,[35] may be those in whom venodilatation and decreased preload is the major determinant of anti-ischemic effect, whereas patients who require higher doses may need more afterload reduction or coronary dilatation in order to improve. Identification of individual characteristics may become mandatory for optimization of nitrate therapy.

In conclusion, our findings appear to indicate that continuous transdermal NTG administration with Deponit 10 patches produces sustained antianginal and anti-ischemic benefits in most patients with stable angina pectoris. These benefits are considerably attenuated at 24 hours after the last application but are still present in some patients. Long-term tolerance and possible advantages over other transdermal NTG preparations have not been addressed in this work and need investigation in other long-term or comparative studies.

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Acute and Chronic Efficacy of 10 mg of Nitroglycerin Patch in Stable Angina Pectoris

DŽENANA E. REZAKOVIĆ, MD, PhD, and JANEZ ŠTALEC

In a single-blind placebo-controlled study, acute and chronic efficacy and duration of action over 24 hours with a 10-mg nitroglycerin (NTG) patch was studied in 24 patients with stable angina pectoris. NTG patch effects were evaluated by means of a multistage treadmill exercise test. During the acute study, exercise tests were performed after the washout period, after placebo patch (5 hours postdosing) and NTG patch (5, 16, 20 and 24 hours postdosing); a 3-day washout period preceded each test. After 3 months of therapy with the NTG patch, exercise tests were performed in 3-day intervals of continuous therapy 5, 16, 20 and 24 hours after patch application. Then, after 7 days of placebo patch therapy, 1 exercise test was performed 5 hours after application. Statistics were obtained by multivariate analysis of difference. Placebo acute and chronic tests did not show any significant difference when compared. Acute and chronic NTG patch tests, (5 to 24 hours) showed significant improvement of maximal exercise time, the time to onset of 1.0 mm ST-depression and to onset of angina as well as maximal ST depression and ST depression 3 and 6 minutes after exercise testing compared with placebo. These effects were significant over 24 hours after acute or continuous therapy, although all values started to decrease after 16 hours, with a decrease of 10% during the acute and of 15% during the chronic period, compared with values at 5 hours. The efficacy was maintained during 3 months of chronic therapy, even with slightly greater magnitude compared with acute administration, mainly during the time of the first angina and 1.0 mm of ST depression. This study revealed exercise efficacy of significant magnitude and a 24-hour duration of action of a 10-mg NTG patch during single and 3-month administration in patients with stable angina pectoris.

(Am J Cardiol 1988;61:52E–58E)

Transdermal nitroglycerin (NTG) patch efficacy, especially during chronic therapy, and duration of action over 24 hours are the prerequisite characteristics for this formulation to be accepted for long-term therapy in patients with stable angina pectoris.

This study investigates the efficacy and duration of action of 10 mg of the NTG patch over a 24-hour period during acute and chronic administration.

Methods

Patients: Twenty-four men (average age 53.5 years) with chronic stable angina pectoris were included in the study. This group was selected according to criteria of the Food and Drug Administration from patients with stable exertional angina pectoris, reproducible during multistage treadmill exercise testing with horizontal or downsloping ST-segment depression of ≥2.0 mm and ≥80-ms duration after the J point in either lead V_5 or another chest lead, performed in the washout period.

All patients had angina pectoris for 18 to 96 months and ≥5 anginal attacks per week; no change in the severity or frequency of attacks in the preceding 3 months had been observed. The status of the disease was stable during the trial. All patients had good responsiveness of chest pain to sublingual NTG. The electrocardiogram at rest showed normal ST segment and sinus rhythm. No patient had had unstable angina pectoris or myocardial infarction within the preceding 6 months. The diagnosis of coronary artery disease had been confirmed by the documentation of acute myocardial infarction in 22 patients 18 to 60 months before the study, and in 18 patients by coronary angiography demonstrating significant luminal diameter narrowing

From the Polyclinic of Cardiology, Department of Medicine, University Hospital, Faculty of Medicine, Faculty of Sciences and Mathematics, Computing Center, University of Zagreb, Zagreb, Yugoslavia.

Address for reprints: Dženana E. Rezaković, MD, PhD, Assistant Professor of Medicine, Associate Research Professor, 41 000 Zagreb, Proleterskih Brigada 222/II, Yugoslavia.

of at least 1 major coronary artery. Exclusion criteria were angina at rest or evidence of coronary artery spasm during angiography. No patient was treated for hypertension, chronic heart failure, severe renal or hepatic disease, atrioventricular or intraventricular conduction disturbances, Lown class III or IV ventricular arrhythmias, or severe diabetes or anemia. The study was performed on ambulatory patients who had given informed consent before entry. The study was approved by the hospital ethics committee.

Study design: The trial was a single-blind placebo-controlled study (Fig. 1). After being gradually withdrawn from previous therapy (within 7 days), patients performed 2 exercise tests to confirm ST-segment inclusion criteria (depression ≥2.0 mm) and to check that the reproducibility between the 2 tests did not vary more than 15%. Afterward, the trial began with a 3-day washout period, without any therapy apart from sublingual NTG capsules (0.8 mg) in case of anginal attacks; an exercise test was performed on the fourth day. Then, after a second 3-day washout period, 1 placebo patch was applied and an exercise test performed after 5 hours. Afterward, 3 washout periods of 3 days' duration were introduced. At the end of each period, a 32-cm^2 patch, releasing 10 mg of NTG was applied for 24 hours and an exercise test performed 5, 16, 20 and 24 hours after administration. After this acute period, 3 months of therapy was begun with 1 NTG patch (10 mg/24 hours). At the end of this period, 1 exercise test was performed 5, 16, 20 and 24 hours after dosing, with 3 days between each test and maintaining continuous patch therapy. This period was followed by 7 days of placebo patch therapy, administered in single-blind manner; an exercise test was performed 5 hours after patch application. Exercise tests were always performed in the morning.

No patient was taking any other drug except NTG (10 mg/24-hour patches) and sublingual NTG (0.8 mg of Deponit® and Perlinganit,® Schwarz GmbH) during the study. The patients were instructed to take off a previous patch and to apply a new one immediately at the scheduled time, without any nitrate-free interval. To perform morning exercise tests 16 and 20 hours after application, the patients had instructions for patch administration at a certain time to ensure a trial design during the acute test and to provide continuous patch therapy 3 days before testing during the chronic period. The patches were placed on a cleaned hairless part of the thorax. Sublingual NTG was always omitted on the morning of the exercise test, or if it was indispensable it was not given at least 1 hour before the exercise test. During 3 months of chronic therapy, the patients were examined monthly by a cardiologist and a resting electrocardiogram was recorded. Patients were required to report weekly by telephone for consultation with the medical staff.

NTG-capsule and patch counting with the marked date of application and continuous telephone and personal contact between the medical staff and the patients ensured high patient compliance and rigid adherence to the experimental protocol.

Experimental procedures: Each patient performed a multistage exercise test according to the Bruce protocol at the end of the washout phase and the placebo and NTG patch acute and chronic periods. Tests were performed on computer-assisted treadmill equipment (Viagraph-International Medical Corporation), with continuous data monitoring of heart rate, ST-segment changes and elapsed time during exercise and recovery period at the same time of the day and by the same staff. Patients were instructed to indicate time to onset of the first definite anginal pain and the time (maximal walking time) when the pain became of such severity—angina of "moderate severity" (maximal angina)—that the patient would ordinarily (or normally-usually) stop walking. Patients were instructed to

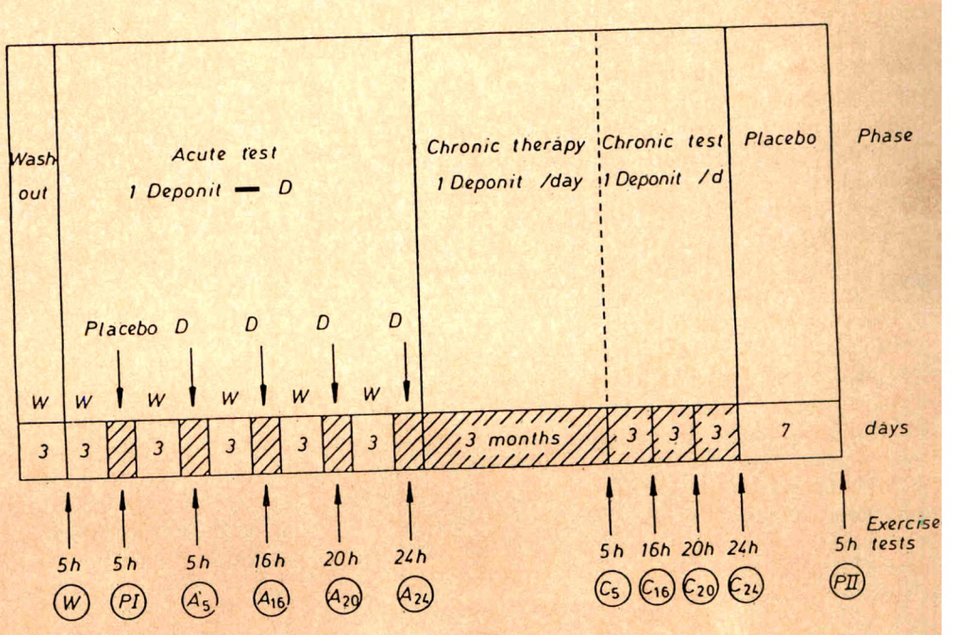

FIGURE 1. Trial design.

TABLE I Variables Used in Multivariate Analysis of Differences

Exercise test:
Maximal walking time (min)
Maximal work load (W/min)
Time to onset of angina pectoris (min)
Time to 1 mm of ST depression (min)
Maximal ST depression (mm)
Severity of maximal angina pectoris (grade 1–4)
ST depression 3 and 6 minutes after exercise test (mm)

TABLE II Significance of Tests Compared with Placebo*

Acute Tests	Chronic Tests
$A_5:P_1$†	$C_5:P_1$†
$A_{16}:P_1$†	$C_{16}:P_1$†
$A_{20}:P_1$†	$C_{20}:P_1$†
$A_{24}:P_1$†	$C_{24}:P_1$†
$W:P_1$†	$P_2:P_1$ NS

* Multivariate analysis of differences.
† $p < 0.01$.
A/C = acute/chronic period 5, 16, 20, 24 hours; A:P = acute compared with placebo test; NS = not significant; P_1/P_2 = placebo periods 1 and 2; W = washout period.

qualify the severity of the first angina and maximal angina, graded as 1 = weak, 2 = moderate, 3 = moderately severe, and 4 = severe. The lead V_5 was monitored on an oscilloscope and its ST segment was recorded throughout the test. Twelve-lead electrocardiograms were obtained at rest, at every 3-minute stage of the test and during a 3- and 6-minute recovery period, as well as at the onset of the first angina, 1.0 mm of ST depression and at angina of moderate severity. The time to onset of 1.0 mm of ST depression and maximal ST depression achieved during moderate angina and during maximal walking time were also recorded. ST-segment depression was also determined during maximal exercise time with placebo, (i.e., common exercise time).

The endpoints of the test were: typical angina of moderate severity, horizontal or downsloping ST-segment depression up to 3.5 mm in the lead in which the most prominent alterations occurred during preliminary testing (usually lead V_5), maximal predicted values of heart rate and walking time, marked dyspnea, no increase in systolic blood pressure in 2 consecutive stages, significant decrease of systolic blood pressure or heart rate, hypertensive reaction, subjective symptoms of cerebral hypoxia, life-threatening arrhythmias and physical exhaustion.

Blood pressure was recorded by sphygmomanometry at rest, at the end of each 3-minute stage of exercise, at onset of first definite angina and at angina of moderate severity, and at 1-minute intervals during a 6-minute recovery period.

All exercise test results were evaluated initally by the testing cardiologist and subsequently by another attending cardiologist who interpreted the tests in a blind manner.

Statistical analysis: Analysis of quantitative and qualitative differences between the washout period, and the periods of placebo or NTG patch acute and chronic therapy was performed by 1 of the multivariate analyses for repeated measurements, the model of differences based on the analysis of the matrix of differences.[1] In this analysis each subject serves as his or her own control. The differences were always calculated toward placebo values as a reference point. The variables used in multivariate analysis are presented in Table I. The significance of statistical analyses was determined at $p < 0.01$. Analyses were performed on the computer Univac 1100.

Results

Analysis of heart rate and blood pressure at rest showed that the NTG patch caused a significant decrease in systolic blood pressure in the first 5 hours (from 142.5 ± 3.6 to 128.8 ± 3.4 mm Hg, $p < 0.01$) and diastolic blood pressure at 5 and 16 hours after acute application (from 87.3 ± 2.6 to 77.1 ± 1.8 and 81.9 ± 1.9 mm Hg, respectively, $p < 0.01$). No change occurred during the other acute or chronic periods over 24 hours.

Exercise heart rate increased in all patients during the acute and chronic period, as well as the values of systolic blood pressure in all periods after the first 5 hours of patch application.

The results of multivariate analysis of exercise tests in the washout and acute or chronic placebo and NTG patch periods are listed in Table II.

Analysis of differences between placebo and washout period showed a significant improvement in maximal walking time (7%), the time to the onset of the first angina (16%) and to 1.0 mm of ST depression (9%) compared with washout values, with insignificant increase in maximal ST-segment depression (2%). Exercise test values obtained during the acute and chronic placebo periods did not differ significantly (Table II, Fig. 2 to 5).

Analysis of differences between results of NTG patch and placebo therapy demonstrated significant improvement of exercise values in all acute and chronic periods of NTG patch therapy compared with placebo. NTG patch treatment during acute and chronic administration demonstrated a significant prolongation in the maximal walking time, the time to onset of the first angina and 1.0 mm of ST depression, with a decrease in the maximal ST depression and ST depression 3 and 6 minutes after the end of exercise testing (Tables II to IV, Fig. 2 to 5).

Exercise improvement was significant after 5 to 24 hours of acute and chronic treatment; however, it was not constant at the same level. Values of the time to onset of the first angina and 1.0 mm of ST segment depression, as well as maximal walking time and ST depression worsened 16 to 24 hours after patch application in the acute phase (range 7 to 14%, mean 10%) and in the chronic period (range 7 to 21%, mean 15%) compared with 5-hour values of acute or chronic period. In contrast, these exercise values were better in the

TABLE III Analysis of Differences Between Placebo 1 (P_1) and Acute (A) Nitroglycerin Patch/10 mg Treatment (5, 16, 20 and 24 Hours) During Exercise Test

	$P_1 - A_5$		$P_1 - A_{16}$		$P_1 - A_{20}$		$P_1 - A_{24}$	
Variables	$\bar{X}$	(D.function)	$\bar{X}$	(D.function)	$\bar{X}$	(D.function)	$\bar{X}$	(D.function)
EXTIME	2.05	0.31	2.03	0.30	1.79	0.31	1.54	0.43
EXWATT	37.83	0.40	37.46	0.39	32.13	0.35	27.42	0.42
$EXTST_1$	3.45	0.51	3.46	0.50	3.23	0.51	2.92	0.60
$EXTAP_1$	3.21	0.58	3.21	0.54	2.90	0.51	2.50	0.56
$EXMST_2$	1.07	0.45	1.06	0.46	0.95	0.47	0.84	0.60
$EXSAP_2$	−1.13	−0.12	−1.08	−0.12	−1.00	−0.14	−0.79	−0.17
EE3ST	0.59	0.54	0.66	0.27	0.57	0.51	0.51	0.64
EE6ST	0.43	0.36	0.46	0.35	0.42	0.32	0.36	0.38
$DF_1 = 8$	p <0.01		p <0.01		p <0.01		p <0.01	
$DF_2 = 16$	F = 191.2		F = 181.0		F = 111.5		F = 113.4	
	MD = 91.6		MD = 86.7		MD = 53.4		MD = 54.3	

D.function = discriminant function; DF = degree of freedom; $EXMST_2$ = maximal ST depression; $EXSAP_2$ = severity of maximal angina; $EXTAP_1$ = time to onset of angina; EXTIME = maximal walking time; $EXTST_1$ = time to 1 mm of ST depression; EXWATT = maximal workload; EE3ST and EE6ST = ST-depression 3 and 6 minutes after exercise test; F = F-test value; MD = Mahalanobis distance; $\bar{X}$ = arithmetic mean of differences between 2 treatments.

Underlined correlation coefficient = p <0.01.

TABLE IV Analysis of Differences Between Placebo 1 (P) and Chronic (C) Nitroglycerin Patch/10 mg Treatment During Exercise Test

	$P_1 - C_5$		$P_1 - C_{16}$		$P_1 - C_{20}$		$P_1 - C_{24}$	
Variables	$\bar{X}$	(D.function)	$\bar{X}$	(D.function)	$\bar{X}$	(D.function)	$\bar{X}$	(D.function)
EXTIME	2.49	0.33	2.43	0.35	2.20	0.45	1.91	0.43
EXWATT	45.71	0.38	44.92	0.40	40.00	0.49	34.25	0.42
$EXTST_1$	4.51	0.56	4.36	0.57	4.03	0.64	3.69	0.61
$EXTAP_1$	4.81	0.51	4.70	0.48	4.04	0.54	3.36	0.49
$EXMST_2$	1.29	0.59	1.20	0.59	1.10	0.65	0.99	0.65
$EXSAP_2$	−2.25	−0.28	−2.21	−0.24	−1.7	−0.25	−1.38	−0.21
EE3ST	0.77	0.66	0.78	0.64	0.71	0.70	0.63	0.57
EE6ST	0.62	0.47	0.61	0.44	0.53	0.53	0.45	0.40
$DF_1 = 8$	p <0.01		p <0.01		p <0.01		p <0.01	
$DF_2 = 16$	F = 251.6		F = 246.5		F = 195.7		F = 92.5	
	MD = 120.5		MD = 118.1		MD = 93.8		MD = 44.3	

Abbreviations as in Table III.

Underlined correlation coefficient p <0.01.

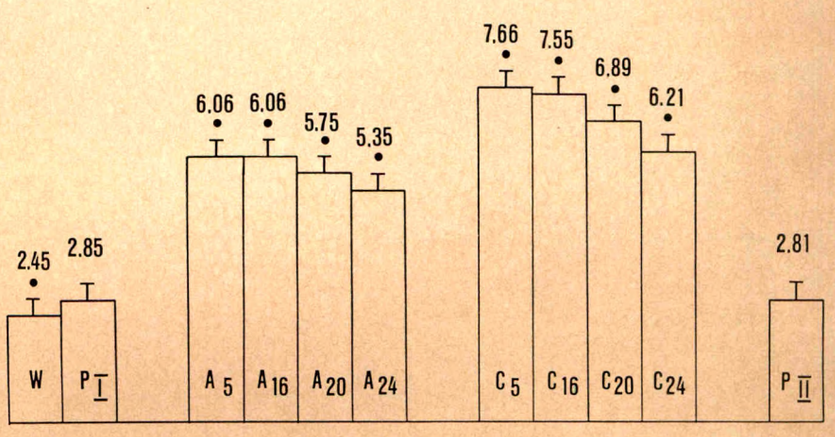

FIGURE 2. Time to onset of angina pectoris (min). ● = p <0.01 compared with placebo value. A/C = acute/chronic (3 months); P = placebo; W = washout; 5, 16, 20 and 24 = hours.

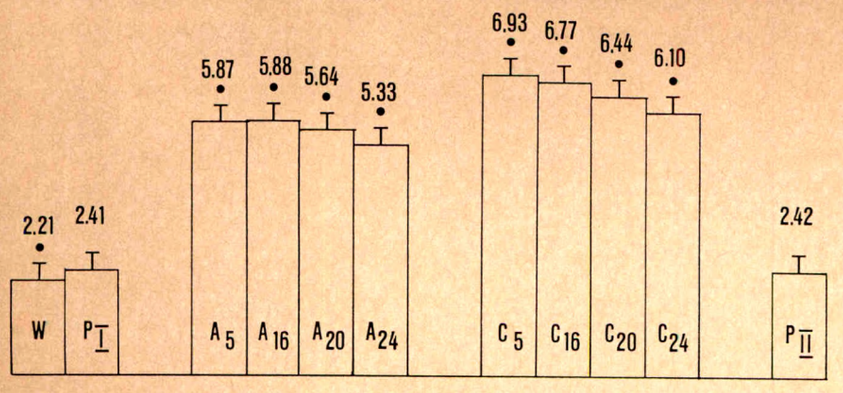

FIGURE 3. Time to 1 mm of ST depression (min). Abbreviations as in Figure 2.

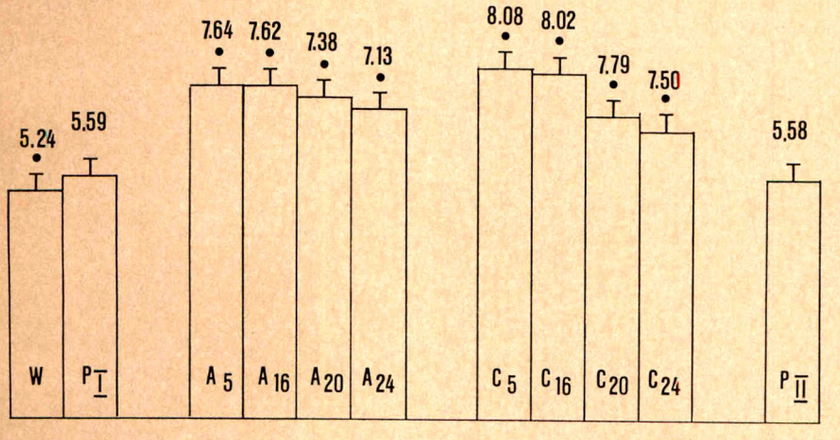

FIGURE 4. Maximal walking time (min). Abbreviations as in Figure 2.

chronic than in the acute period, at 5 hours (range 6 to 26%, mean 16%) and 24 hours (range 5 to 16%, mean 11%) compared with the acute phase (Table V).

Discussion

This study demonstrated significant improvement of antianginal and anti-ischemic exercise efficacy in the patients with stable angina pectoris during acute and chronic therapy with a 10-mg NTG patch—an increase in maximal walking time (range 44 to 34%) and a decrease in maximal ST-segment depression (range 47 to 36%)—over 24 hours compared chronic therapy with placebo. A significant increase in exercise heart rate and systolic blood pressure, during acute and chronic therapy, could be explained by an improvement in ventricular performance.

These results confirmed a sustained 24-hour duration of patch action during acute and chronic administration compared with placebo effect. However, all exercise parameters started to decrease 16 hours after application, so that 24-hour values significantly diminished compared with 5-hour results: average, 10 and 15% during the acute and the chronic periods, respectively. The decrease over 24 hours appears to be greater during the chronic than during the acute period. However, this did not essentially affect the results during the chronic period, because efficacy during continuous 3-month patch therapy was sustained, with even moderately greater magnitude in maximal walking time (by 6 to 5%), in maximal ST depression (by 14 to 8%), in the time to onset of the first angina (by 26 to 16%) and in time to 1.0 mm of ST depression (by 18 to 14%) compared with 5- and 24-hour acute values.

Placebo significantly affected some exercise test parameters, however, with worsening of values for maximal ST depression and ST depression at 3 and 6 minutes after the test; this exercise improvement was probably due to psychological reasons.

Much controversy exists about adequate NTG patch dosage in long-term therapy of angina pectoris; the dilemma being that low-dose (5 to 10 mg/24-hour NTG patch) is too low to ensure magnitude of efficacy, and the recommended high doses appear to induce rapid development of nitrate tolerance over 24-hours and during chronic therapy.

The review of world studies until the spring of 1987[2] showed that 28 publications of 10 mg/24-hour NTG patch acute and chronic exercise efficacy and 24-hour duration of action in 417 patients with stable angina pectoris have been published.

In the acute phase therapy, 11 studies with 197 patients demonstrated significant 10-mg NTG patch efficacy, with duration of action from 21 to 28 hours after administration. These studies had an average of 18 patients per study: in 4 placebo-controlled trials, performed in a double-blind manner (101 patients)[3-6]; in 3 placebo-controlled studies performed in a single-blind manner (46 patients)[7-9]; and in another 4 place-

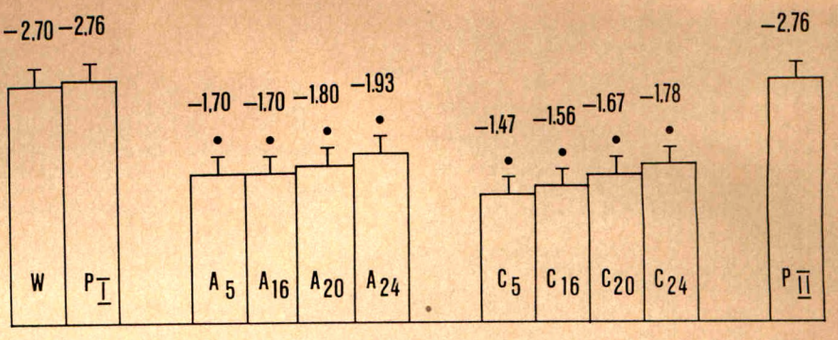

FIGURE 5. Maximal ST-segment depression (mm). Abbreviations as in Figure 2.

bo-controlled or open studies (50 patients).[10-13] However, 7 trials with 86 patients showed an attenuation in the efficacy after 2.5,[14-16] 4,[17,18] 6[19] or 10[20] hours of therapy. These studies (an average of 12 patients in each study) were all conducted in a placebo-controlled double-blind manner. Finally, 1 placebo-controlled double-blind study with 7 patients showed complete absence of efficacy over 24 hours.[21]

In the chronic phase therapy, 7 studies with 131 patients showed long-term (7 days to 12 months) 10 mg/24-hour NTG patch efficacy, with confirmed 24-hour duration of action. These studies had an average of 19 patients, with 2 trials conducted in a placebo-controlled double-blind manner (29 patients),[22,23] 3 in a placebo-controlled single-blind manner (44 patients),[8,24,25] and 2 other studies in a placebo-controlled or open manner (58 patients).[5,10] However, another 6 studies demonstrated either an efficacy only at 2 hours after therapy (1 study with 16 patients[26]) or negative chronic efficacy in any period over 24 hours of testing (5 studies with 74 patients[27-30]). These investigations had an average of 15 patients and all studies were conducted in a placebo-controlled double-blind manner.

Three studies continued acute investigations (78 patients) during chronic 10 mg/24-hour NTG patch therapy for 7 days, 21 days and 12 months, and confirmed that acute exercise effects over 24 hours were sustained during continuous treatment, with unchanged magnitude and duration of action.[5,8,10]

Additional findings of a placebo-controlled single blind comparative double-blind study (10 patients) demonstrated improved metoprolol efficacy with 10 mg/24-hour NTG patch in a 2-day trial.[31]

The results of these studies confirm that 10 mg/24-hour NTG patch therapy demonstrates significant improvement in exercise tolerance during single or continuous administration, with sustained chronic effects and duration of action over 24 hours in more than 50% of the patient population studied. The findings of our study support this conclusion. There is enough evidence that the dose of 10 mg/24-hour NTG patch is not too low and insufficient to produce exercise effects of significant magnitude and 24-hour duration of action during acute and long-term therapy.

However, the controversy still exists, because there are groups of patients with stable angina pectoris who have absence or rapid attenuation of efficacy taking this NTG dosage. Recently, in 2 placebo-controlled double-blind studies (22 patients), in which attenuation developed during continuous 10 mg/24-hour NTG patch therapy, nitrate-free intervals demonstrated that it could be prevented.[32,33]

TABLE V Significance of Tests Comparing Two Intervals*

Comparisons†	Mean Change (%)
$A_{24} < A_5$	10
$C_{24} < C_5$	15
$C_5 > A_5$	16
$C_{24} > A_{24}$	11

* Multivariate analysis of differences.
† $p < 0.01$.
A = acute; C = chronic; 5 and 24 = 5 and 24 hours.

The main problem for future investigations should be to define the reasons why some patients have significant beneficial effect while others demonstrate rapid nitrate tolerance or complete absence of efficacy with continuous low-dose NTG patch therapy.

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Relation of Transdermal Nitroglycerin Efficacy with Dosage in Different Subsets of Patients

DŽENANA E. REZAKOVIĆ, MD, PhD

Two single-blind placebo-controlled studies were consecutively performed with nitroglycerin (NTG) (5 and 10 mg/24 hours) patches in 24 patients with stable angina pectoris. The relation of NTG patch efficacy with dosage and different subsets of patients during acute and chronic patch therapy was analyzed. NTG patch effects were assessed by multistage treadmill exercise test at 5, 16, 20 and 24 hours after patch application, during single patch administration and after 3 months of continuous therapy, with washout phases as well as with 1- and 7-day placebo patch periods. The analysis of differences between NTG and placebo patch demonstrated significant improvement of exercise capacity in the total group of 24 patients. A taxonomy analysis revealed 2 different subsets in the sample of 24 patients, having similar exercise ST depression but different exercise walking times in the washout period. Group I (15 patients), with an initial 68% of maximal predicted time, showed moderate increases in magnitude of exercise efficacy during the acute and chronic period, with low decrease of effects over 24 hours. Efficacy was greater during the chronic phase, with evident dose relation of all changes. Group II (9 patients), with 40% of maximal predicted time, demonstrated an increased efficacy during acute and chronic therapy, with a steep decrease of all values over 24 hours and significant improvement of exercise tolerance during chronic therapy; these changes were not mainly dose-related. These differences in the magnitude and in the pattern of exercise efficacy over 24 hours, during acute and chronic NTG patch therapy, could probably be attributed to different nitrate mechanisms of action, depending on the pathophysiologic characteristics of stable angina pectoris in 2 subsets of patients. The controversies about NTG patch efficacy have been discussed with regard to relation between multiple modes of nitrate action and the subsets of patients with different prevailing mechanisms of stable angina pectoris.

(Am J Cardiol 1988;61:59E–69E)

The controversies about transdermal nitroglycerin (NTG) efficacy are still unresolved. Studies of confirmed clinical efficacy during chronic therapy and of duration of action from 12 to 24 hours, as well as those with no evidence or insufficient effects in stable angina pectoris have been reported simultaneously. The questions about adequate NTG dosage and duration and magnitude of antianginal and anti-ischemic efficacy still wait for scientific answers.[1,2]

The analysis of the relation of NTG patch dosage and different clinical subsets of patients with the magnitude and the pattern of exercise efficacy, as well as with the duration of patch action in stable exertional angina pectoris was performed on the results of 2 studies. These trials were consecutively performed, first with 5 and then with 10 mg/24 hours of NTG during acute and chronic administration.[3,4]

From the Polyclinic of Cardiology, Department of Medicine, University Hospital, Faculty of Medicine, University of Zagreb, Zagreb, Yugoslavia.

Address for reprints: Dženana E. Rezaković, MD, PhD, Assistant Professor of Medicine, Associate Research Professor, 41 000 Zagreb, Proleterskih brigada 222/II, Yugoslavia.

Methods

Patients: Twenty-four men (average age 53.5 years) with stable angina pectoris (according to Food and Drug Administration classification) were included in the study. These patients were selected from a group with stable exertional angina pectoris reproducible during multistage exercise testing. They had horizontal or downsloping ST-segment depression of ≥2.0 mm and 80 ms in duration after the J point in either lead V_5 or another chest lead. Tests were performed in the washout period. The patients had ≥5 anginal attacks per week and all confirmed good responsiveness of chest pain to sublingual NTG. These patients had no change in severity or frequency of attacks in the preceding 3 months and the status of disease was stable during the trials. The electrocardiogram at rest showed normal ST segment. Angina pectoris had been present

from 18 to 96 months. No patient had unstable angina or myocardial infarction within the preceding 6 months. Ischemic heart disease had been confirmed in 22 patients, with acute myocardial infarction 18 to 60 months before the study, and in 20 patients with evidence of significant luminal diameter stenoses of at least 1 major coronary artery seen on coronary angiography. Exclusion criteria were angina at rest or evidence of coronary artery spasm during angiography. No patient was treated for hypertension, chronic heart failure, severe renal or hepatic disease, atrioventricular or intraventricular conduction disturbances, ventricular arrhythmias (Lown class III or IV), severe diabetes or anemia. The study was performed on ambulatory patients who had given informed consent before entry. The study was approved by the hospital ethics committee.

Study design: Two studies, each having an acute and chronic 3-month period, were consecutively performed in a single-blind placebo-controlled design in 24 patients with stable coronary heart disease. The first trial was performed with 5 mg/24-hour NTG patches and a second time with 10 mg/24-hour NTG patches.

After being gradually withdrawn from previous therapy (within 7 days), the patients performed 2 exercise tests to confirm ST-segment inclusion criterion (depression of ≥2.0 mm) and to check that the reproducibility between 2 tests did not vary more than 15%. Afterward, all patients had a 3-day washout period, without any therapy except sublingual NTG (0.8 mg) in case of anginal attack. Patients performed an exercise test on the fourth day. Then, after a second 3-day washout period, 1 placebo patch was applied and an exercise test performed after 5 hours. Afterward, acute testing with 5 mg/24-hour NTG patch at 5, 16, 20 and 24 hours after application was performed on 4 separate days, with a 3-day washout period preceding each NTG patch application. After this acute period, 3 months of therapy were introduced with one 5 mg/24-hour NTG patch each day. At the end of this phase, exercise testing was performed at 5, 16, 20 and 24 hours after administration on 4 separate days, with 3 days of continuous therapy between each test. This period was followed by 7 days of placebo patch therapy in a single-blind manner; an exercise test was performed 5 hours after patch administration at the end of this phase (Fig. 1). After this trial, the complete design was repeated, beginning with exercise testing after a 3-day washout period, followed by acute and chronic administration of 10 mg/24-hour NTG and placebo patches. Both trials were performed over 10 months for each patient.

During the study no patient was taking any other drug except NTG (5 and 10 mg/24-hour patches) and sublingual NTG (0.8 mg of Deponit® and Perlinganit®, Schwarz GmbH). A placebo patch was similar in size and form to the NTG patch. The patients were instructed to take off a previous patch and to apply a new one immediately at the scheduled time, without any nitrate-free interval. To perform 16- and 20-hour exercise tests during the morning, the patients had instructions for patch administration at a certain time, to ensure trial design during acute testing and to provide continuous patch therapy 3 days before testing during the chronic period. The patches were put on a cleaned and hairless part of the thorax. Sublingual NTG was always omitted on the morning of the exercise test, or if it was indispensable it was not given at least 1 hour before the exercise test. During each period of 3 months of chronic therapy, the patients were examined monthly by a cardiologist who recorded an electrocardiogram at rest. They were instructed to telephone weekly for consultation with the medical staff.

NTG-capsule and patch counting with marked date of application and continuous telephone and personal contact between the medical staff and the patients ensured high patient compliance and rigid adherence to the experimental protocol.

Experimental procedures: Each patient performed a multistage exercise test according to the Bruce protocol at the end of the washout phase, and the placebo and NTG patch acute and chronic periods. Tests were

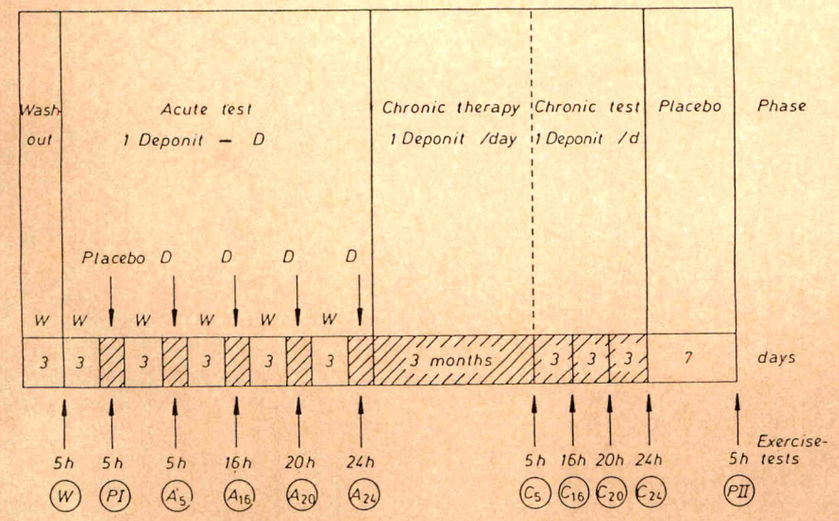

FIGURE 1. Trial design.

performed on computer-assisted treadmill equipment (Viagraph-International Medical Corporation), with continuous data monitoring of heart rate, ST-segment changes and elapsed time during exercise and recovery period, at the same time of the day and by the same staff. The patients had been instructed to indicate time to onset of the first definite angina and time (maximal walking time) when the pain became of such severity—angina of "moderate severity" (maximal angina)—that the patient would ordinarily stop walking. The patients were instructed to qualify the severity of the first and maximal angina, graded as 1-weak, 2-moderate, 3-moderately severe, and 4-severe. The lead V_5 was monitored on an oscilloscope and its ST segment was recorded throughout the test. The 12-lead electrocardiogram was obtained at rest, at every 3-minute stage of the test and during a 3- and 6-minute recovery period, as well as at the onset of angina, at the onset of 1.0 mm ST depression and when angina became of moderate severity. The time to onset of 1-mm of ST-segment depression and maximal ST depression during moderate angina and at maximal walking time were also recorded. ST-segment depression was also determined at placebo maximal exercise time (i.e., common maximal exercise time).

The endpoints of the test were typical angina of moderate severity, horizontal or downsloping ST-segment depression up to 3.5 mm in the lead in which the most prominent alterations occurred in preliminary tests (usually lead V_5), maximal predicted values of heart rate and walking time, marked dyspnea, no increase in systolic blood pressure in 2 consecutive stages, significant decrease of systolic blood pressure or heart rate, hypertensive reaction, subjective symptoms of cerebral hypoxia, life-threatening arrhythmias and physical exhaustion.

Blood pressure was recorded by sphygmomanometry at rest, at the end of each 3-minute stage of exercise, at onset of angina and during moderate angina and at 1-minute intervals during the 6-minute recovery period.

All exercise test results were evaluated initially by the testing cardiologist and subsequently by another attending cardiologist who interpreted the tests blindly.

Statistical analysis: Analysis of quantitative and qualitative differences between the washout period and the placebo or NTG patch acute and chronic periods of therapy was performed with one of the multivariate analysis for repeated measurements. The model of differences was based on the analysis of the matrix of differences.[3-5] The differences were always calculated toward placebo values as a reference point.

Testing of the hypothesis that a group of 24 patients had been constituted by different subsets of patients was performed by analysis of taxonomy[6] on 4 exercise test variables: time to the onset of angina and to the onset of 1 mm of ST depression, maximal walking time and maximal ST depression. The criteria of aggregation was the minimization of mean distance between the classes of variables. This analysis demonstrated the aggregation of the patients in 2 groups (1 group with 15 patients and 1 group with 9 patients) relating to washout values of these variables.

Analysis of differences between placebo and NTG patch values in previous 4 exercise variables for each of 2 groups of patients was performed again with the multivariate analysis of differences.

Analysis of differences in 4 exercise variables among 2 groups of patients for washout, placebo and NTG patch acute and chronic periods was performed with multivariate analysis of variance and discriminant analysis.[7]

The significance of statistical analysis was determined at $p < 0.01$. Analysis were performed on a Univac 1100 computer.

Results

The aim of analysis was to investigate the relation of NTG patch dose and potentially different subsets of patients with magnitude and pattern of exercise efficacy over 24 hours during acute and chronic administration.

The analysis of differences between the washout, placebo and NTG patch periods in all exercise test values (Table I) in the total group of 24 patients revealed a significant difference between placebo and 5, 16, 20 and 24 hours of NTG patch (5 and 10 mg) acute and chronic periods. These results were reported in 2 previous publications (Table II).[3,4] An insight to overall exercise test changes during NTG patch therapy compared with placebo is best demonstrated by Mahalanobis distances: the distance between placebo and each acute or chronic exercise test centroid, in multivariate analysis of difference (Fig. 2). Exercise test results during all periods with both NTG patch doses were signif-

TABLE I Variables Used in Multivariate Analysis of Differences

Exercise test:
Maximal walking time (min)
Maximal work load (W/min)
Time to onset of angina pectoris (min)
Time to 1 mm of ST depression (min)
Maximal ST depression (mm)
Severity of maximal angina pectoris (grade 1–4)
ST depression 3 and 6 minutes after exercise test (mm)

TABLE II Significance of Tests Compared with Placebo in 24 Patients*

Acute Test	Chronic Test
A_5: P_1†	C_5: P_1 †
A_{16}: P_1†	C_{16}: P_1†
A_{20}: P_1†	C_{20}: P_1†
A_{24}: P_1†	C_{24}: P_1†
W: P_1†	P_1: P_2 NS

* Multivariate analysis of differences.

† $p < 0.01$.

A/C = acute/chronic period compared with placebo test by multivariate analysis; NS = not significant; P_1/P_2 = placebo periods 1 and 2; W = washout period.

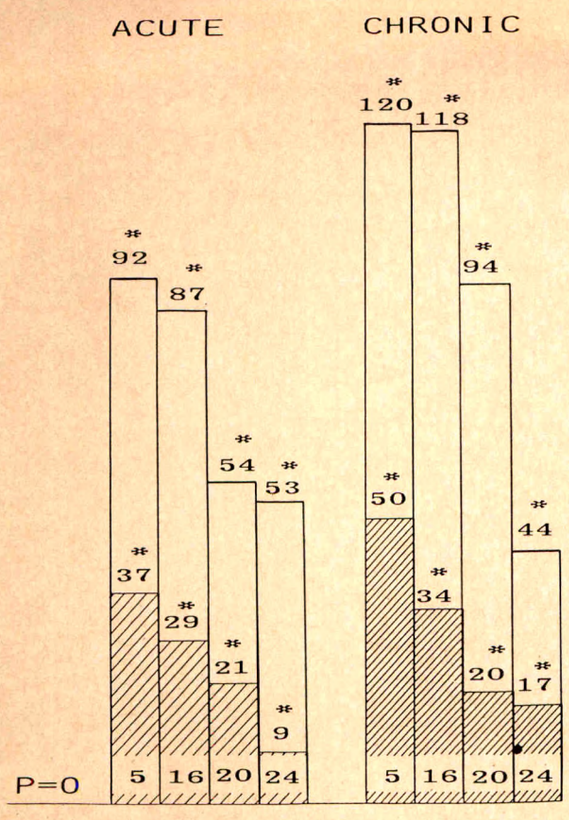

FIGURE 2. Mahalanobis distances of acute and chronic nitroglycerin patch exercise values from placebo centroid. P = placebo value; 5, 16, 20 and 24 = hours; *p <0.01 acute and chronic values (5, 16, 20 and 24 hours) compared with placebo; *shaded bars* = nitroglycerin 5 mg/24 hours; *open bars* = nitroglycerin 10 mg/24 hours.

icantly better than those with placebo. However, this improvement gradually diminished from 5 to 24 hours; results were poorer after 24 hours compared with results after 5 hours although still significant. It is obvious that exercise test results in all periods are better with 10 mg than with 5 mg of NTG. It is of interest to emphasize that exercise improvement was more sustained in the first 16 hours with the 10-mg NTG patch than with the 5-mg patch. The effects of the 5-mg patch started to decrease sharply 5 hours after administration.

A more detailed analysis of the dose relation and exercise improvement showed that the 10-mg NTG dose had better effects in all presented variables, especially in the time to onset of angina and 1 mm of ST depression. Furthermore, the difference between 5- and 24-hour values with both dosages was higher during the chronic period. However, the decrease in all values during 24-hour acute and chronic therapy, calculated as a percentage of 5-hour values, was greater with the 10-mg NTG patch (Table III).

Exercise values during chronic therapy with both NTG dosages were significantly better compared with those during the acute period. This improvement was mainly in a prolongation of the time to onset of angina and to onset of 1 mm of ST depression. However, the dose effect was not seen any more and the improvement was similar for both dosages (Table IV).

Testing the hypothesis of different subsets within the group of 24 patients was performed by taxonomy analysis showing an aggregation of patients in 2 groups, one with 15 and the other with 9 patients. This aggregation was formed relating to the following exercise variables: time to onset of angina and 1 mm of ST

TABLE III Percent of Changes in Acute and Chronic 5- and 10-mg Nitroglycerin Patch Exercise Results at 5, 16, 20 and 24 Hours Compared with Placebo Values in 24 Patients

	Acute (hours)				% of Change	Chronic (hours)				% of Change
Variables	5	16	20	24	A_{24}/A_5	5	16	20	24	C_{24}/C_5
Maximal walking time	21%*	21%	18%	15%	−5%	29%	28%	24%	21%	−6%
(min)	37%†	36%	32%	27%	−7%	44%	43%	39%	34%	−7%
% of change 10/5 mg patch	+11	+12	+12	+10		+12	+12	+12	+10	
Maximal ST depression	23%	24%	20%	18%	+7%	30%	30%	25%	23%	+10%
(mm)	39%	39%	35%	30%	+14%	47%	43%	40%	36%	+21%
% of change 10/5 mg patch	−19	−18	−17	−13		−22	−18	−18	−14	
Time to 1.0 mm ST depression	56%	60%	53%	46%	−6%	88%	88%	79%	73%	−8%
(min)	143%	144%	134%	121%	−9%	187%	181%	167%	153%	−12%
% of change 10/5 mg patch	+64	+61	+61	+59		+61	+57	+57	+54	
Time to first angina	49%	54%	43%	36%	−8%	83%	81%	69%	67%	−9%
(min)	113%	113%	102%	88%	−12%	169%	165%	142%	118%	−19%
% of change 10/5 mg patch	+48%	+43%	+46%	+43%		+52%	+52%	+49%	+35%	

All values are $p < 0.01$ compared with placebo value.
* 5 mg/24 hours patch values.
† 10 mg/24 hours patch values.
A_5, A_{24} and C_5, C_{24} = 5 and 24 hours of acute and chronic therapy, respectively.

depression, maximal walking time and maximal ST depression. Each of these groups showed significant improvement in the previous 4 exercise variables with 5 and 10 mg NTG patches, compared with placebo (Table V). The further analysis of the differences, by the multivariate analysis of variance and discriminant analysis between 2 groups, revealed that they significantly differed in several characteristics.

First, these groups were significantly different at initial washout exercise status, demonstrating that with similar maximal ST-segment depression, group II had a significantly shorter time to onset of angina, 1 mm of ST depression and maximal walking time (Tables VI and VII). In addition, 2 groups demonstrated significantly different magnitude and pattern of efficacy in all acute and chronic 5- or 10-mg patch periods.

Group I had moderate exercise improvement with both patch dosages, especially in the time to onset of angina and 1 mm of ST depression, with a relatively low percentage of decrease at 24 hours compared with 5-hour values. A decrease in values at 24 hours was slightly higher during the chronic phase than during the acute phase (Tables VI to VIII). The improvement during the chronic period was demonstrated only in the prolongation of the time to onset of angina and 1 mm of ST depression, compared with the acute phase (Table IX). The effect of the higher 10-mg dosage was obviously more important as seen with the magnitude of exercise improvement and in the greater decrease of values at 24 hours compared with the 5-mg dose during the acute and chronic periods. However, the dose relation was not evident in the magnitude of improvement during the chronic phase compared with the acute period; it was similar for both dosages (Tables VI to IX, Fig. 3 and 4).

Group II had similar decreases in maximal ST-segment depression, but much greater improvement in maximal walking time, and time to onset of angina and onset of 1 mm of ST depression with both patch dosages; there were steep decreases of all values over 24 hours during the acute and chronic periods, although they remained significant compared with values during placebo therapy. A difference between the values at 5 and 24 hours was similar to group I; it was slightly higher during the chronic phase than during the acute phase (Tables VI to VIII). Furthermore, this group had greater increase not only in the time to onset of angina and 1 mm of ST depression, but also in maximal walking time during the chronic period with both dosages compared with results during the acute period (Table IX). The dose relation was maintained only in greater exercise efficacy with the 10-mg patch therapy, whereas there was no longer any dose relation in the decrease during 24 hours in the acute and chronic periods and in the improvement of exercise time during the chronic period compared with the acute phase; values were similar for both dosages (Table VI to IX, Fig. 3 and 4).

When the groups were analyzed according to 24-hour duration of 15% increase in maximal walking time beyond washout values (which was the limit of prestated variability) 11 patients in group I who received the 5 mg patch achieved this magnitude of efficacy during the acute and chronic periods. Another 4 patients could not reach this value over 24 hours during the acute period. Two of them also did not reach it during the chronic period, whereas 2 patients achieved this limit during chronic therapy. Twelve patients had similar results with the 10-mg patch over 24 hours during the acute and chronic periods. Another 3 patients did not reach this limit during the acute period. Two of them also did not reach it during the chronic period, whereas 1 patient achieved this limit during chronic therapy.

In group II, prestated magnitude of efficacy was not achieved only by 2 of 9 patients with the 5-mg patch during the acute period, whereas all of them showed adequate response in the chronic phase. However all 9 patients with the 10-mg patch increased their maximal walking time to more than 15% during the acute and chronic periods.

TABLE IV Percent of Improvement During Chronic 5 and 24 Hours Compared with Acute Values in 24 Patients

Variables	C_5/A_5 %	C_{24}/A_{24} %	Mean % of Change
Maximal walking time			
5 mg†	6*	5*	+6
10 mg†	6*	5*	+6
Maximal ST depression			
5 mg	−10*	−7*	−9
10 mg	−14*	−8*	−11
Time to 1.0 mm of ST depression			
5 mg	20*	18*	+19
10 mg	18*	14*	+16
Time to first angina			
5 mg	23*	23*	+23
10 mg	26*	16*	+21

* $p < 0.01$ multivariate analysis.
† NTG patch 5 and 10 mg/24 hours
A = acute; C = chronic; 5/24 = 5 and 24 hours

TABLE V Multivariate Analysis of Differences: Significance of Exercise Test Compared with Placebo in Groups I and II

Acute Test	Chronic Test
A_5: P*	C_5: P*
A_{16}: P*	C_{16}: P*
A_{20}: P*	C_{20}: P*
A_{24}: P*	C_{24}: P*

*$p < 0.01$.
A = acute; C = chronic; 5, 16, 20, 24 = hours; P = placebo.

Discussion

These results show that exercise improvement in the whole group of 24 patients achieved not only statistical significance, but also clinically important magnitude of efficacy during acute and chronic therapy in the prolongation of maximal walking time, the time to onset of angina and 1 mm of ST depression, with de-

TABLE VI Analysis of Differences in Exercise Test Results Between Two Responder Groups of Patients, During 5-mg Nitroglycerin Patch Acute and Chronic Therapy (at 5 and 24 hours Postdosing), in Washout and Placebo Patch Periods

Variables	Washout	Placebo	Acute (5 hours)	Acute (24 hours)	% of Change A_{24}/A_5	Chronic (5 hours)	Chronic (24 hours)	% of Change C_{24}/C_5
Group I								
Maximal walking time (min)	6.25* ± 0.95	6.64 ± 0.86	7.63 ± 0.78	7.55 ± 0.74	−1	8.01 ± 0.84	7.85 ± 0.75	−2
Maximal ST depression (mm)	−2.52 ± 0.23	−2.66 ± 0.27	−2.01 ± 0.21	−2.07 ± 0.30	+3	−1.79 ± 0.22	−1.92 ± 0.33	+7
Time to 1.0 mm of ST depression (min)	3.11 ± 0.81	3.23 ± 0.81	4.57 ± 0.86	4.52 ± 0.87	−1	5.31 ± 0.77	5.21 ± 0.85	−2
Time to first angina (min)	3.33 ± 0.83	3.74 ± 0.84	5.21 ± 0.61	5.11 ± 0.70	−2	6.15 ± 0.62	5.99 ± 0.90	−3
Mean percentage					$\bar{X}$ = 2%			$\bar{X}$ = 4%
Group II								
Maximal walking time (min)	3.57 ± 0.98	3.88 ± 1.01	5.39 ± 0.84	4.61 ± 1.24	−14	6.02 ± 0.75	5.02 ± 0.96	−17
Maximal ST depression (mm)	−2.83 ± 0.43	−2.80 ± 0.40	−2.23 ± 0.29	−2.50 ± 0.36	+12	−2.02 ± 0.23	−2.34 ± 0.31	+16
Time to 1.0 mm of ST depression (min)	0.75 ± 0.38	0.74 ± 0.37	1.90 ± 0.58	1.37 ± 0.55	−28	2.63 ± 0.78	1.88 ± 0.62	−29
Time to first angina (min)	0.79 ± 0.37	1.11 ± 0.46	2.21 ± 0.52	1.47 ± 0.67	−33	3.16 ± 0.74	2.28 ± 0.85	−28
Mean percentage					$\bar{X}$ = 22%			$\bar{X}$ = 23%
$DF_1 = 4$ $DF_2 = 19$	p <0.01	p <0.01	p <0.01	p <0.01		p <0.01	p <0.01	

* Initial numbers are the arithmetic mean ($\bar{x}$).
All values are expressed as mean ± standard deviation.
All p values are probability of significance in multivariate analysis of variance and discriminant analysis.
DF = degree of freedom.

TABLE VII Analysis of Differences in Exercise Test Results Between Two Responder Groups of Patients, During 10-mg Nitroglycerin Patch Acute and Chronic Therapy (at 5 and 24 hours Postdosing), in Washout and Placebo Patch Periods

Variables	Washout	Placebo	Acute (5 hours)	Acute (24 hours)	% of Change A_{24}/A_5	Chronic (5 hours)	Chronic (24 hours)	% of Change C_{24}/C_5
Group I								
Maximal walking time (min)	*6.08 ± 1.05	6.66 ± 0.90	8.38 ± 0.90	8.03 ± 1.06	−4%	8.67 ± 1.00	8.31 ± 1.02	−4%
Maximal ST depression (mm)	−2.60 ± 0.25	−2.65 ± 0.22	−1.61 ± 0.20	−1.78 ± 0.24	+11%	−1.41 ± 0.14	−1.67 ± 0.20	+18%
Time to 1.0 mm of ST depression (min)	3.01 ± 0.89	3.29 ± 0.99	6.78 ± 1.07	6.43 ± 1.04	−5%	7.60 ± 1.10	7.01 ± 1.11	−8%
Time to first angina (min)	3.35 ± 0.92	3.81 ± 0.95	7.09 ± 1.07	6.49 ± 1.12	−8%	8.25 ± 1.04	7.44 ± 1.03	−10%
Mean percentage					$\bar{X}$ = 7%			$\bar{X}$ = 10%
Group II								
Maximal walking time (min)	3.68 ± 0.80	3.91 ± 0.98	6.41 ± 0.80	5.63 ± 1.09	−12%	7.11 ± 0.90	6.14 ± 0.92	−14%
Maximal ST depression (mm)	−2.88 ± 0.38	−2.95 ± 0.41	−1.84 ± 0.27	−2.17 ± 0.20	+18%	−1.57 ± 0.19	−1.95 ± 0.21	+24%
Time to 1.0 mm of ST depression (min)	0.88 ± 0.40	1.12 ± 0.50	4.34 ± 0.74	3.50 ± 0.85	−20%	5.81 ± 0.82	4.60 ± 0.89	−21%
Time to first angina (min)	0.97 ± 0.39	1.26 ± 0.54	4.34 ± 0.80	3.44 ± 0.82	−21%	5.90 ± 0.90	4.17 ± 0.87	−29%
Mean percentage					$\bar{X}$ = 18%			$\bar{X}$ = 22%
$DF_1 = 4$ $DF_2 = 19$	p <0.01†	p <0.01	p <0.01	p <0.01		p <0.01	p <0.01	

* Initial numbers are the arithmetic mean ($\bar{x}$).
† probability of significance in multivariate analysis of variance and discriminant analysis.
All values are expressed as mean ± standard deviation.
DF = degrees of freedom.

TABLE VIII Percent of Changes in Acute and Chronic 5- and 10-mg Nitroglycerin Patch Exercise Results, in Two Responder Groups of Patients Compared with Placebo Values

Variables	Acute (hours) 5	16	20	24	Mean % of Change 10/5 mg	Chronic (hours) 5	16	20	24	Mean % of Change 10/5 mg
Maximal walking time										
Group I										
5 mg	15%	15%	15%	14%		21%	20%	19%	18%	
10 mg	26%	26%	23%	21%		30%	30%	28%	25%	
% of change (10/5 mg)	+10	+10	+10	+6	+9	+8	+9	+8	+6	+8
Group II										
5 mg	39%	38%	27%	19%		55%	48%	38%	29%	
10 mg	64%	62%	54%	44%		82%	77%	67%	57%	
% of change (10/5 mg)	+19	+18	+22	+22	+20	+18	+20	+22	+22	+21
Maximal ST depression										
Group I										
5 mg	25%	26%	23%	22%		33%	32%	28%	28%	
10 mg	39%	40%	36%	33%		53%	44%	40%	37%	
% of change (10/5 mg)	−20	−18	−18	−14	−18	−21	−18	−17	−13	−17
Group II										
5 mg	20%	20%	15%	13%		28%	28%	21%	16%	
10 mg	38%	37%	32%	27%		47%	43%	39%	34%	
% of change (10/5 mg)	−18	−16	−16	−13	−16	−22	−18	−19	−17	−19

creases in maximal ST depression with the 5- and 10-mg NTG patch.[3,4,8] These trials indicated significant 24-hour duration of action, but with a decrease in all values 16 hours after application, resulting in lower exercise values at 24 hours (7 to 14% and 7 to 21%) during the acute and chronic period with the 5- and 10-mg patch. All these changes were dose-related, since magnitude of exercise improvement and decrease of efficacy over 24 hours (higher during the chronic period than during the acute period) were greater with the 10-mg patch. Despite a decrease in values over 24 hours, improvement was greater during chronic 5- and 10-mg patch periods compared with acute values. The average percent increase during the chronic phase was 6% and 6% in maximal walking time; in maximal ST depression 9% and 11%; in time to onset of angina 23% and 21%; and in 1 mm of ST depression 19% and 16%, respectively, for each NTG dose. These changes were obviously dose-independent.

The analysis of 2 subsets of patients revealed that they were not homogeneous in all exercise parameters, although maximal ST-segment depression of ≥2.0 mm during the washout exercise test had been determined as inclusion criteria, to minimize variability and to achieve homogeneity of patients. ST depression was similar in the 2 groups, but maximal walking time and time to onset of angina and 1 mm of ST depression were significantly different; these findings indicate that they were essentially different in functional cardiovascular capacity. Since the groups were different at initial status, the differences in therapeutic response could be expected.

Group I patients had significantly higher maximal exercise time (mean 6.25 minutes to 7.14 METs, equal to 68% of maximal predicted walking time for 50- to 59-year-old men) as well as the time to onset of angina and 1 mm of ST depression. They responded with the 5- and 10-mg patch, with moderate augmentation of efficacy, greater for maximal ST depression (24 to 30%, 37 to 44%) than for maximal walking time (15 to 20%, 24 to 29%) during the acute and chronic periods. The magnitude of exercise decrease was low over 24 hours during the acute and chronic periods (mean 2 to 4% with the 5-mg dose and 7 to 10% with the 10-mg dose). Greater magnitude of efficacy and decrease over 24 hours during the acute and chronic periods were dose-related to the 10-mg patch. However, during chronic NTG patch therapy, limited improvement of exercise tolerance compared with the acute phase, was evident only in prolongation of the time to onset of angina (average 18 and 16%) and 1 mm of ST depression (average 16 and 11%) with 5- and 10-mg NTG being obviously dose-independent.

Group II patients had very low initial values in maximal walking time (mean 3.7 minutes, 5.14 METs equal to 40% of maximal predicted value) and time to onset of angina and 1 mm of ST depression. These patients responded (with 5 and 10 mg) with significantly greater magnitude of efficacy in maximal walking time (31 to 43%, 56 to 71%), whereas the change in maximal ST depression (17 to 23%, 34 to 41%) was similar in group I during the acute and chronic periods. The magnitude of exercise decreased markedly over 24 hours during the acute and chronic periods (mean 22 to 23% with 5-mg patch and 18 to 22% with 10-mg patch), with similar difference in percentage of decrease between acute and chronic periods as it was in group I. However, despite the marked decrease in

TABLE IX Percent of Improvement at Chronic 5 and 24 Hours Compared with Acute Values in Group I and II Patients

Variables	Group I			Group II		
	C_5/A_5	C_{24}/A_{24}	Mean % of Change	C_5/A_5	C_{24}/A_{24}	Mean % of Change
Maximal walking time						
5 mg†	5%	4%	+5	12%*	9%*	+11
10 mg†	3%	3%	+3	11%*	9%*	+10
Maximal ST depression						
5 mg†	11%*	7%	−9	11%*	6%	−9
10 mg†	12%*	6%	−9	15%*	10%*	−13
Time to 1 mm of ST depression						
5 mg†	16%*	15%*	+16	38%*	37%*	+38
10 mg†	12%*	9%*	+11	34%*	31%*	+33
Time to first angina						
5 mg†	18%*	17%*	+18	43%*	55%*	+49
10 mg†	16%*	15%*	+16	36%*	21%*	+29

* $p < 0.01$ multivariate analysis.
† Nitroglycerin patch 5 and 10 mg/24 hours.
A = acute; C = chronic; 5/24 = 5 and 24 hours;

values over 24 hours, the increase in exercise tolerance during chronic therapy compared with the acute period was much higher than in group I, with prolongation of maximal walking time (average 11 and 10%) and improvement in time to onset of angina (average 38 and 33%) and 1 mm of ST depression (average 49 and 29%) with both doses. The augmentation of exercise values in this group evidently was only partly dose-related. However, major improvement in maximal walking time, time to onset of angina and 1 mm of ST depression, especially with augmented values during chronic therapy and marked decreases in all parameters over 24 hours. However, major improvement in maximal walking time, time to onset of angina and 1 mm of ST depression, especially with augmented values during chronic therapy and marked decrease in all parameters over 24 hours, may be caused by mechanisms independent of NTG dosage.

The characteristics of these 2 groups of patients define them as different responders with the NTG patch, with different magnitude of efficacy during acute and chronic therapy and different patterns of action over 24 hours and during chronic treatment. The response of group I was characterized by moderate magnitude of efficacy and low decrease of effects over 24 hours, evidently a dose-related phenomenon, whereas limited increase of efficacy during chronic therapy did not show this relation. There was a higher probability that values in group I patients could not reach more than 15% beyond washout values (the prestated value of variability) because of moderate magnitude of efficacy. In fact, 27 and 13% of patients with the 5-mg patch and 20 and 13% of patients with the 10-mg patch during acute and chronic therapy did not have these values over 24 hours. In contrast, group II showed important magnitude of efficacy, with a marked decrease of values over 24 hours and significant improvement of exercise tolerance during the chronic period, with clear evidence that these changes were not mainly NTG dose-dependent. There was an absence of a 24-hour duration of action in 22% of patients in group II only with the acute 5-mg patch, with confirmed efficacy during chronic therapy. All patients in this group reached the prestated limit of exercise variability during acute and chronic therapy with the 10-mg patch.

These differences in the magnitude and in the pattern of efficacy could probably be attributed mainly to different mechanisms of nitrate action, underlying their beneficial effects, which are likely to differ depending on the pathophysiologic characteristics of the patients with stable angina pectoris. These analyses revealed several parallel changes during nitrate therapy, an improvement of effort tolerance over 24 hours after single or continuous patch administration, a decrease of efficacy over 24 hours (of greater magnitude during chronic therapy), and finally the increase of efficacy during chronic therapy, compared with effects after single patch administration. The final magnitude of efficacy and duration of NTG patch action probably reflects as a resultant all these changes, depending on the mode of nitrate action, the prevailing mechanisms and the genesis of myocardial ischemia.

A study of 217 patients with confirmed coronary artery disease showed the complexity of responses to sublingual isosorbide dinitrate, with improvement of exercise tolerance in 43% of patients having the higher rate-pressure product and in 12% with reduction of rate-pressure product, while 18% of patients had no improvement.[9] These results support the view that nitrates exert their beneficial effects by different modes of action, an increase in coronary blood flow or a reduction of myocardial oxygen demand, depending on the underlying mechanisms of stable angina pectoris.

The patients in groups I and II significantly differed in initial exercise capacity; this finding indicates that they probably had different pathogenetic mechanisms responsible for their symptoms. The magnitude and the quality of NTG efficacy in group I appeared to be related to NTG dosage, whereas in group II, the magni-

tude and pattern of NTG effects were supposedly modified by the characteristics of patients themselves. No further investigations were performed to determine the prevailing mechanism of nitrate action. However, based on the differences in improvement of efficacy, especially with chronic therapy, group I probably had an increase in coronary reserve and group II a reduction in myocardial oxygen demand, although a certain degree of mixed action could not be excluded. Several studies have shown that chronic nitrate therapy in congestive heart failure was associated with a significant increase in effort tolerance, especially in submaximal exercise by a reduction of pulmonary capillary pressure and left ventricular pressures and by effects of repeated physical training.[10,11] Although the patients in our study did not have congestive heart failure, the exercise-induced elevation of left ventricular pressures could not be excluded in all patients, since they had severe stable angina pectoris. The improvement of the magnitude of exercise duration in group II patients—especially in submaximal levels seen as a major increase in time to onset of angina and 1 mm of ST depression as well as the independence of these changes to NTG dosage—support the assumption that it was due to preload reduction and to a decrease of myocardial oxygen demand.

Some contradictory results in NTG patch studies are probably the result of different subsets of patient samples included in the investigations. The review of all investigations of low-dose NTG patch (5 and 10 mg/24-hour) acute or chronic 24-hour exercise efficacy in patients with stable angina pectoris, performed in a placebo-controlled double-blind design, revealed altogether 26 publications with 431 patients until the spring of 1987.

Acute 24-hour investigations demonstrated in 7 studies of 151 patients (mean 22) exercise efficacy of 16

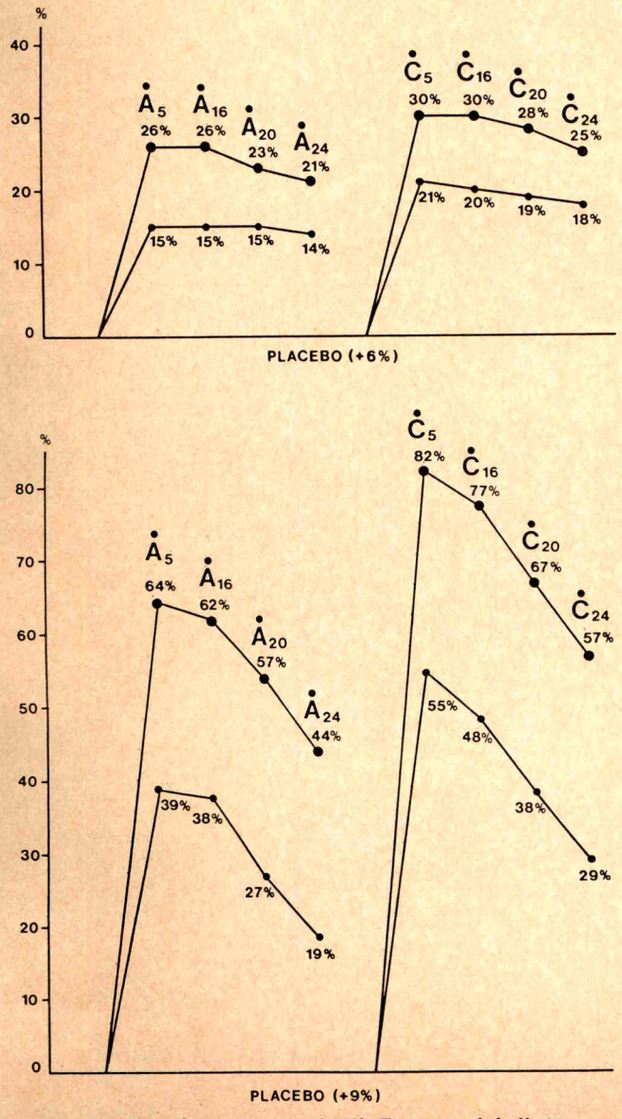

FIGURE 3. Maximal walking time (min). *Top*, group I; *bottom*, group II. *Small dots*, nitroglycerin (5 mg/24 hours). *Large dots*, nitroglycerin (10 mg/24 hours). A/C = p <0.01 acute and chronic values (5, 16, 20 and 24 hours) compared with placebo. % = percentage of change compared with placebo value.

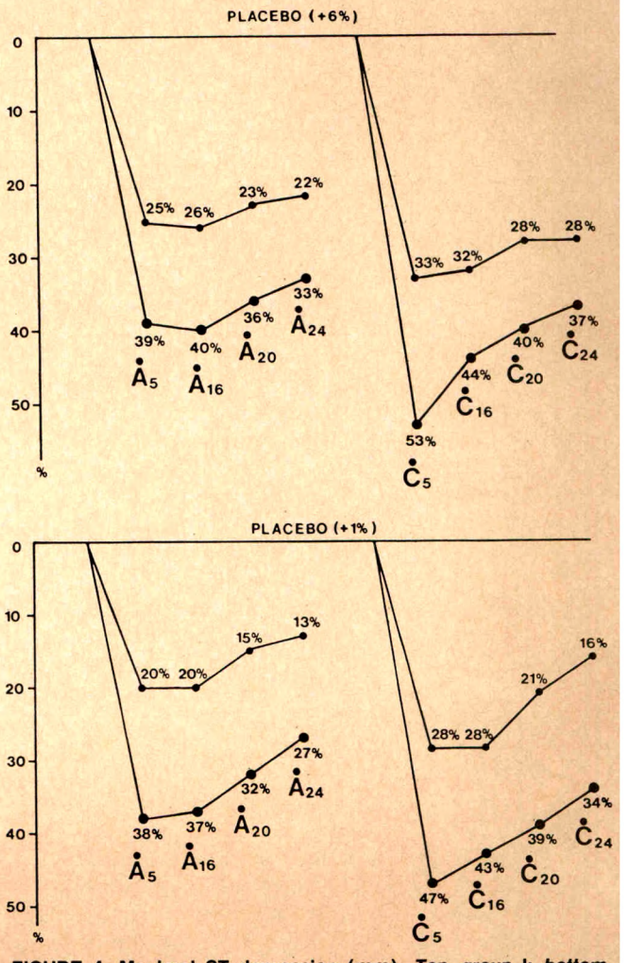

FIGURE 4. Maximal ST depression (mm). *Top*, group I; *bottom*, group II. See Figure 3 for explanation of symbols.

to 24 hours' duration,[12-18] in 9 trials of 104 patients (mean 12) attenuation of efficacy at 2 to 3 hours,[19-22] 4 to 6 hours[23-26] and 10 hours[27] after patch application. One study of 7 patients revealed complete absence of any 24-hour effect.[28]

Chronic investigations confirmed in 4 studies of 79 patients (mean 20), positive exercise efficacy over 24 hours during 7, 14 and 17 days of continuous therapy.[13,29-31] Seven trials of 110 patients (mean 16) showed either an efficacy only at 2 hours after therapy (1 study)[37] or complete absence of any efficacy over 24 hours.[32-36]

One study of 40 patients, performed in placebo-controlled double-blind design during the acute period with positive exercise efficacy over 24 hours, was continued in an open trial and demonstrated sustained efficacy with a 24-hour duration of action during 12 months of continuous therapy with the 10 mg/24- hour NTG patch.[18]

This short review of trials of the same design, testing 24-hour duration of action and exercise efficacy with low doses (5 to 10 mg/24-hour patch) demonstrated contradictory results after single patch or chronic therapy. Placebo-controlled single-blind or open trials with the same NTG patch dosage showed the same discrepancies.[38]

Similarly, the analysis of some placebo-controlled double-blind randomized crossover studies, with 5 and 10 mg/24-hour NTG patch showing overall positive exercise efficacy after 7 to 14 days of continuous therapy, revealed that 58% of 40 and 57% of 52 patients achieved maximal exercise duration increase of more than 15% beyond the washout values (being the prestated variability).[39,40]

Any effort to compare or pool the results of different studies is complex and difficult, with many possibilities that may bias the conclusions of an entire population of patients,[41] but certain assumptions could be drawn from our and other cited trials.

There are supposedly multiple responses in the quality and quantity of NTG patch therapy among different samples of patients, as well as within 1 group of patients. It could be concluded that about half of the studied patients show statistically significant exercise improvement, with moderate to important clinical magnitude of efficacy, with sustained long-term effects and 24-hour duration of action with 5 to 10 mg/24-hour NTG patch therapy. The magnitude and pattern of action of these effects could be related to NTG dosage and to the characteristics of patients themselves; probably to the prevailing mechanisms of stable angina pectoris. However, there are patients without any evidence of NTG patch efficacy; in most studies it is not clear if this inefficacy is due to a failure to achieve therapeutic NTG blood levels with this method of NTG dosage, or if it is due to absence of NTG responsiveness. Finally, there are patients with attenuation of NTG patch efficacy (probably due to rapid development of nitrate tolerance) who could profit from intermittent dosing with nitrate-free intervals.[42,43]

It is not possible in a moment to define the conclusions about NTG patch efficacy, which could be generalized to the entire population of patients with stable angina pectoris. It is obviously necessary to titrate NTG patch dosage and regimen of therapy individually to each patient, taking into consideration the variety of potential NTG responses. Future trials should be designed to respond to the multiple, complex and contradictory phenomena occurring during NTG patch acute and chronic therapy. Finally, further investigations of NTG patch efficacy should define the homogeneous subsets of patients based on the prevailing mechanisms of cornary artery disease and assess its relation to the responses of NTG patch therapy.

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Intravenous Isosorbide Dinitrate During Open-Heart Surgery and Its Role in the Treatment of Right-Sided Congestive Heart Failure.

R. SIMON PARSONS, MA, BM, BCh, FFARCS

Recent awareness of the importance of the functional integrity of the right ventricle and the effect of raised pulmonary vascular resistance on cardiac output after cardiopulmonary bypass has focused attention on means of protecting right ventricular myocardium and reducing right ventricular afterload during open-heart surgery.

A study of the acute effects of bolus intravenous isosorbide dinitrate (ISDN) has shown that after cardiopulmonary bypass, bolus intravenous ISDN produced highly significant ($p < 0.001$) decreases in mean pulmonary arterial pressure (13%), pulmonary vascular resistance (23%) and the ratio of pulmonary to systemic vascular resistance (20%), indicating that active pulmonary vasodilation had occurred in the absence of other hemodynamic changes. The results suggest that possibly the acute effect of low-dose ISDN after cardiopulmonary bypass is predominantly exerted on the right ventricular afterload if systemic arterial pressure is not elevated. Two different clinical situations are described in which intravenous ISDN proved beneficial, one being acute pulmonary hypertension after protamine sulphate and the second being acute right-sided congestive heart failure with systemic hypotension unresponsive to conventional therapeutic measures. Thus, ISDN may prove a useful agent for alleviating right ventricular dysfunction at a time of not infrequent cardiovascular instability, the period after bypass. (Am J Cardiol 1988;61:70E–73E)

During open-heart surgery, preservation of the functional integrity of the left ventricle has received widespread attention. However, right ventricular dysfunction in the perioperative period due to inadequate myocardial protection or other causes is being recognized more frequently and its importance accepted as a major cause of the limitation of cardiac output after cardiopulmonary bypass.[1,2] The addition of raised right ventricular afterload from pulmonary hypertension to the poor function of a damaged right ventricle may aggravate right ventricular dysfunction and can constitute a considerable therapeutic challenge.

Systemic vasodilator agents, when used to reduce pulmonary vascular resistance, may tend to produce systemic hypotension and consequently reduce coronary artery perfusion pressure.[3] Cardiac output may be reduced by systemic vasodilators in patients with a raised pulmonary vascular resistance. However oral isosorbide dinitrate (ISDN) has been reported to exert a favorable effect on pulmonary artery pressure and vascular resistance without producing undesirable severe systemic adverse effects.[4] A study of the effects of bolus injections of ISDN during open-heart surgery was performed to assess the acute effects of intravenous ISDN after cardiopulmonary bypass on the pulmonary and systemic circulations.[5] The results of this study encouraged the application of intravenous ISDN to the treatment of right-sided congestive heart failure (CHF) after cardiopulmonary bypass.

From the Department of Anaesthetics, The United Medical and Dental Schools of Guy's and St. Thomas' Hospitals, Guy's Hospital, London, England.

Address for reprints: R. Simon Parsons, FFARCS, Department of Anaesthetics, The United Medical and Dental Schools of Guy's and St. Thomas' Hospitals, Guy's Hospital, St. Thomas Street, London SE 1 9RT, England.

Use of Isosorbide Dinitrate by Bolus Injection

In a study of the effects of intravenous ISDN in 15 adult patients undergoing open heart surgery,[5] after standard premedication (lorazepam administered orally, followed by diamorphine and hyoscine administered intramuscularly), general anesthesia was induced and maintained with diazepam and fentanyl, with relaxation for intubation and ventilation with

100% oxygen to normocapnia provided by pancuronium and d-tubocurarine.

The response to ISDN before and after cardiopulmonary bypass was determined by various points of relative cardiovascular stability. Hemodynamic parameters and cardiac output were measured immediately before and at 3 to 5 minutes after an intravenous bolus of ISDN (0.25 to 0.3 mg).

Table I summarizes the acute effect of an intravenous bolus of ISDN (0.25 to 0.3 mg) on measured variables after cardiopulmonary bypass. After cardiopulmonary bypass, there were significant decreases in mean pulmonary artery pressure (13%) and in indexed pulmonary vascular resistance (23%), similar to results before bypass; however, there were no significant changes found in mean systemic artery pressure, indexed systemic vascular resistance or pulmonary capillary wedge pressure. The ratio of pulmonary to systemic vascular resistances was reduced by 20%. Right ventricular stroke work index was reduced by 15% in the absence of significant changes in cardiac index or right atrial pressure. Table II summarizes the analysis of the data after division into 2 groups according to the preexisting mean pulmonary artery pressure before administration of ISDN. In both groups, mean pulmonary artery pressure, indexed pulmonary vascular resistance and the pulmonary to systemic vascular resistance ratio decreased significantly and the percent changes were similar between the groups.

After this study, intravenous ISDN was administered when pulmonary hypertension had occurred or right-sided CHF had developed after cardiopulmonary bypass. An example of the first situation occurred after injection of protamine sulphate after cardiopulmonary bypass. The cardiovascular responses of 2 patients undergoing coronary artery revascularization, 1 of whom was receiving ISDN by constant intravenous infusion (2 mg/hour), were studied and the effect of ISDN on acute pulmonary hypertension was demonstrated. The cardiovascular responses of both patients, with an obvious systemic hypotensive episode commencing 15 seconds after the start of injection of protamine sulphate in the untreated patient, followed 15 seconds later by a prolonged pulmonary arterial hypertensive response that took more than 20 minutes to recover, are shown in Figure 1. In contrast, the patient treated with ISDN showed delayed and simultaneous systemic hypotensive and pulmonary hypertensive responses commencing 40 seconds after the start of protamine sulphate injection, the pulmonary hypertension being reduced by an additional bolus of ISDN (0.5 mg) (as shown) and returning to the original levels in approximately 3 minutes. The effect of intravenous ISDN on acute right-sided CHF in a patient undergoing coronary artery revascularization is shown in Figure 2. The systemic arterial blood pressure after cessation of cardiopulmonary bypass remained inadequate despite infusion of dobutamine and repeated injections of methoxamine. Right ventricular contraction was poor, the right ventricle dilated and right atrial pressure increased steadily as shown. After the failure to improve with inotropic support and methoxamine the patient received intravenous ISDN (0.3 mg) and within 30 seconds the right ventricular contraction improved, systemic arterial pressure then increased and right atrial pressure decreased. After another bolus dose of intravenous ISDN, the rate of infusion of dobutamine was reduced and the patient had an uneventful recovery.

TABLE I Values After Bypass Surgery in 15 Patients

	Before ISDN	After ISDN
MPAP (mm Hg)*	24.8 ± 2.5	21.6 ± 2.4
MAP (mm Hg)	69.7 ± 1.9	69.7 ± 2.0
HR (beats/min)	95.2 ± 3.3	95.0 ± 3.4
RA (mm Hg)	7.4 ± 0.6	7.3 ± 0.6
PCWP (mm Hg)	11.0 ± 0.7	10.6 ± 0.9
PVRI (dynes s/cm^5 m^2)*	397.9 ± 48.0	308.4 ± 43.6
SVRI (dynes s/cm^5 m^2)	1,963.9 ± 111.4	1,964.0 ± 123.4
CI (liters/min/m^2)	2.68 ± 0.1	2.71 ± 0.1
RVSWI (g · m/beat/m^2)†	7.5 ± 1.4	6.4 ± 1.6
LVSWI (g · m/beat/m^2)	23.1 ± 1.6	23.6 ± 1.7
PVRI/SVRI (%)*	23.3 ± 3.7	18.6 ± 3.3

*$p < 0.001$; † $p < 0.005$.

All values are expressed as mean ± standard error of the mean.

CI = indexed cardiac output; HR = heart rate; LVSWI = left ventricular stroke work index; MAP = mean systemic arterial pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PVRI = indexed pulmonary vascular resistance; PVRI/SVRI = ratio of pulmonary to systemic vascular resistance; RA = right atrial pressure; RVSWI = right ventricular stroke work index; SVRI = indexed systemic vascular resistance.

TABLE II Results Grouped According to Mean Pulmonary Artery Pressure

	Before ISDN	After ISDN
MPAP >25 mm Hg (n = 12)		
MPAP (mm Hg)	51.6 ± 6.5	45.7 ± 6.3
PVRI (dynes s/cm^5 m^2)	900.3 ± 113.2	724.6 ± 90.3
PVRI/SVRI (%)	51.6 ± 5.4	42.3 ± 4.7
MPAP <25 mm Hg (n = 32)		
MPAP (mm Hg)	16.7 ± 0.8	14.2 ± 0.7
PVRI (dynes s/cm^5 m^2)	251.3 ± 15.8	178.3 ± 13.7
PVRI/SVRI (%)	11.3 ± 0.8	8.5 ± 0.8

Values are expressed as mean ± standard error of the mean.

$p < 0.001$.

Abbreviations as in Table I.

Discussion

In the initial study,[5] the effects of intravenous ISDN were primarily on the right ventricle and pulmonary circulation, with no significant effects on the left ventricle and systemic circulation. In all cases, pulmonary vascular resistance decreased regardless of the level of pulmonary artery pressure. Furthermore, the decrease in pulmonary artery pressure and vascular resistance appeared unrelated to the preexisting pulmonary artery pressure. The lack of systemic effects may be related to the lack of systemic hypertension in these patients or may reflect the low dose of ISDN used in contrast with a previous study in which high-dose

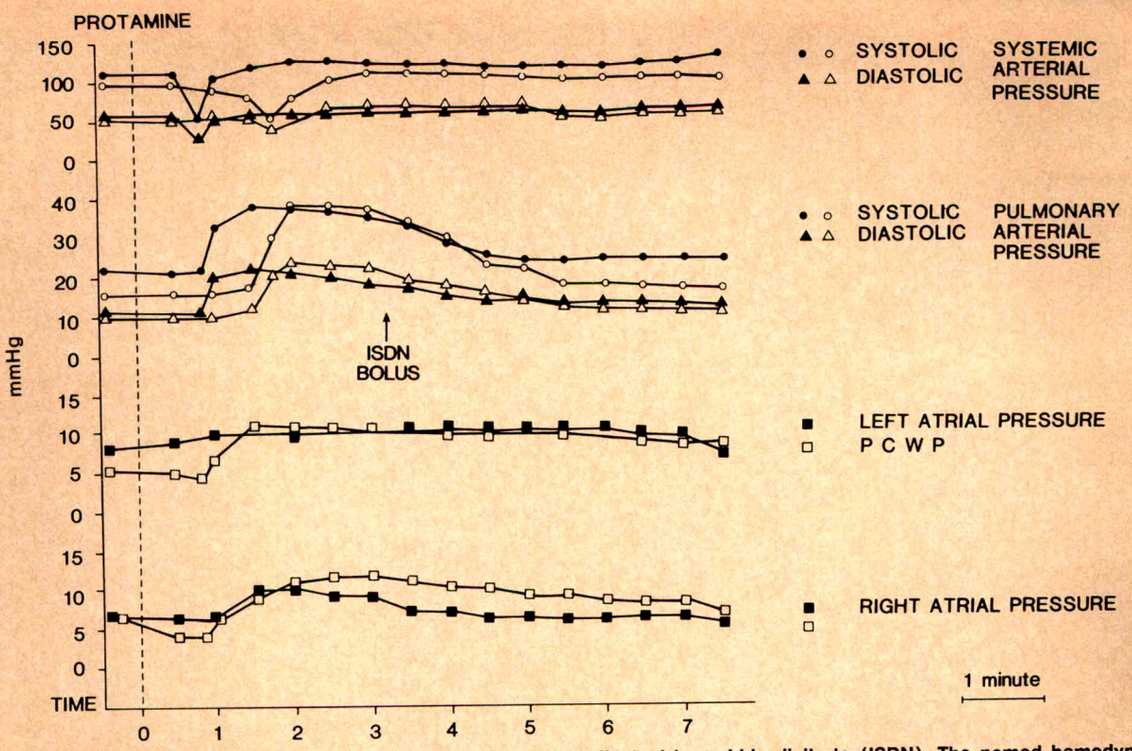

FIGURE 1. Hemodynamic responses to protamine sulphate and the effect of isosorbide dinitrate (ISDN). The named hemodynamic measurements for the patient treated with ISDN are shown with *open symbols* and those of the untreated patient with *closed symbols*. PCWP = pulmonary capillary wedge pressure.

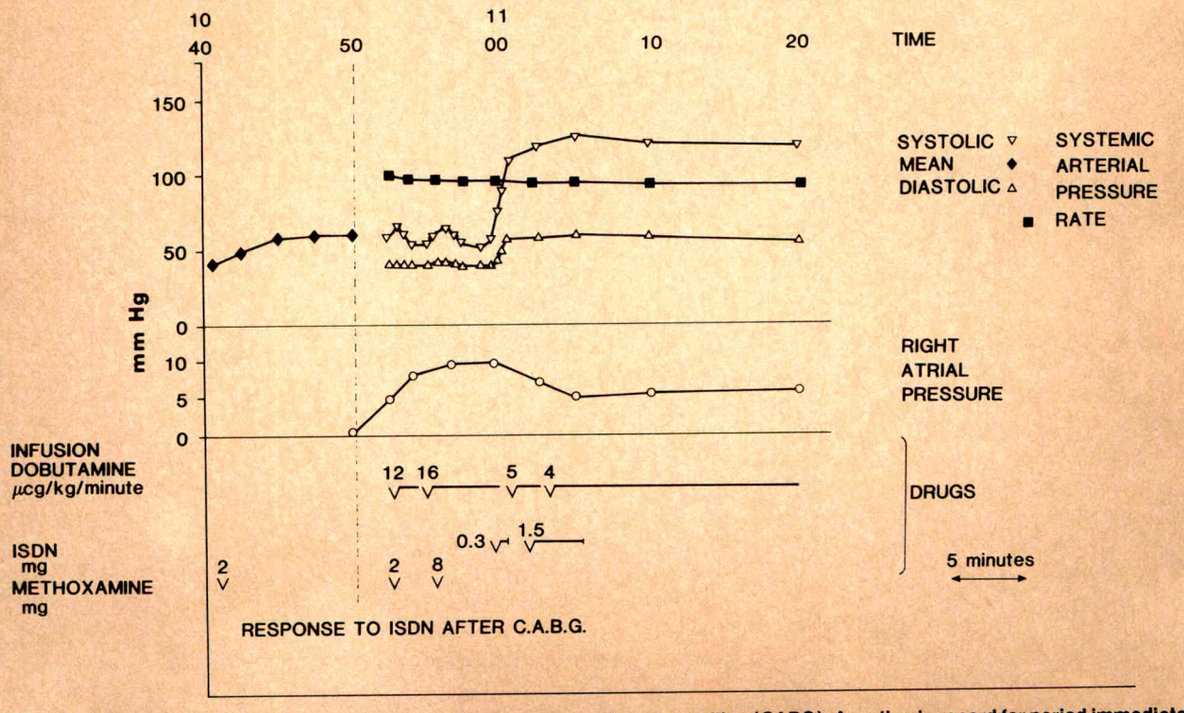

FIGURE 2. Response to isosorbide dinitrate (ISDN) after coronary artery bypass grafting (CABG). Anesthesia record for period immediately before and after cessation of coronary artery bypass grafting is indicated by a *dotted vertical line* at 1050 hours.

ISDN (up to 10 μg/kg/min) was used specifically for control of systemic hypertension.[6] Additionally, the reduction of pulmonary to systemic vascular resistance ratio indicated a predominantly pulmonary vasodilator effect.[7]

The reduction in right ventricular afterload in the apparent absence of systemic adverse effects suggests 2 possible roles for ISDN after cardiopulmonary bypass:

The first application may be in the management of pulmonary hypertension, which may be part of the original disease process or may follow the administration of protamine sulphate. Severe reactions to protamine sulphate are unusual but ISDN may attenuate an acute pulmonary hypertensive response without causing systemic hypotension. In addition, elevation of pulmonary vascular resistance that has been reported after cardiopulmonary bypass[8] in the absence of adverse reactions to protamine sulphate, may aggravate preexisting right ventricular dysfunction.

The second application may be found after severe right-sided CHF (Fig. 2). This reveals the paradox of a nitrate vasodilator being a good vasopressor by improving myocardial function. There may be many causes of right ventricular dysfunction,[1] which may be related to poorer myocardial protection of the right than the left ventricle during periods of aortic cross-clamping. Right ventricular failure may critically limit cardiac output even when a left ventricular mechanical assist device is in use.[9]

An agent that reduces right ventricular afterload and also improves coronary artery blood flow without reducing systemic arterial pressure would appear to be the appropriate treatment of right ventricular dysfunction. There may be a place for the prophylactic administration of ISDN from the period before bypass to achieve optimal biventricular performance and improve coronary arterial blood flow before and during a potentially highly stressful time for both ventricles, the early period after bypass.

Acknowledgment: I thank Philip B. Deverall for his kind permission to study the patients under his care and the laboratory technicians of the Department of Clinical Physiology for assistance with hemodynamic monitoring and blood gas analysis.

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Effects of Long-Term Treatment with 120 mg of Sustained-Release Isosorbide Dinitrate and 60 mg of Sustained-Release Nifedipine on Myocardial Perfusion

BEATRICE STEGARU, MD, REINHARD LOOSE, MD, HELMUT KELLER, MD, JAN BUSS, MD, and EDUARD WETZEL, MD

Forty patients with coronary artery disease and scintigraphically proven myocardial ischemia were randomized into 2 groups receiving 4 weeks of treatment with either 120 mg of isosorbide dinitrate (ISDN) release or 60 mg of nifedipine release. Control exercise testing and myocardial scintigraphy were continued until anginal pains occurred, and repeated at identical individual workloads at the end of the 4 weeks of drug therapy. Myocardial scintigrams were evaluated by quantitative recording of counts in 60 segments/frame.

Twenty patients in the ISDN group (group I) exhibited 47 significantly ischemic areas. The remaining 20 patients (group II), treated with nifedipine, had 50 ischemic areas before therapy. In the ischemic areas in group I, there was a mean difference of 30.9% between counts at rest and during exercise in the pretreatment period, and a difference of 18.1% after therapy (39.0%). In group II, the pretreatment difference was 28.8%, decreasing to 20.6% after therapy (17.8%). Both groups of patients were subsequently subdivided into 3 subsets: (1) significantly improved perfusion, (2) significant worsening, and (3) unchanged myocardial perfusion. Group I had 59.5% of areas with significant improvement and 10.6% of areas with significant worsening. In 29.7% of the areas, the findings were unchanged. Group II had improvement in 40% of areas, of significantly worsened areas in 6%, and unchanged areas in 54%, in both groups myocardial ischemia was reduced by therapy, but ISDN improved myocardial perfusion to a considerably greater extent than did nifedipine.

(Am J Cardiol 1988;61:74E–77E)

The antianginal effects of isosorbide dinitrate (ISDN) and nifedipine were proven by a large number of studies published since the 1970s, demonstrating the increase in exercise capacity, reduction of frequency of angina as well as of ST-segment depression during exercise. A direct coronary dilating effect was demonstrated for both drugs. In addition, the hemodynamic effects of both drugs, consisting of preload by nitrates and afterload reduction by nifedipine, led to an improvement of myocardial perfusion.[1-3]

Methods

In this study, 40 patients with angiographically proved coronary artery disease were randomized into 2 groups of 20 each and treated for 4 weeks either with 120 mg of sustained-release ISDN or 60 mg of sustained-release nifedipine.

Before and after therapy, the weekly anginal frequency, ST-segment depression during exercise, double product (heart rate × blood pressure) during exercise and response of myocardial ischemia were analyzed. Individual maximal exercise to angina before treatment was repeated after 4 weeks of drug therapy and the results were compared. Myocardial scintigrams were recorded after a washout period before treatment and after 4 weeks of therapy with either drug, 1 hour after the last dose. The scintigrams were interpreted with the aid of a semiquantitative, computerized count analysis. Immediately after the exercise tests and after a 2-hour rest period, 3 scintigrams were recorded in the anterioposterior and 30° and 70° left anterior oblique projections. The data aquisition was performed with 600.000 counts/frame. The background was substracted with a linear interpolation in a circle (region of interest) using the modified algorithm

From the I. Medical Clinic, Cardiology, Institute of Radiology, Klinikum Mannheim, University of Heidelberg, West Germany.

Address for reprints: Beatrice Stegaru, MD, I. Medical Clinic, Cardiology, Klinikum Mannheim, Theodor-Kutzer-Ufer, 6800 Mannheim, West Germany.

of Goris et al.[4] The noise reduction was obtained with a 2-dimensional 9-point Gauss filter. After selection of the center of the left ventricle determined by the operator, the radial transformation was performed with 60 sectors (6-degree steps) in counterclockwise direction, starting at 3 o'clock. The normalized circumferential profiles for all 6 projections (3 early and 3 late) were displayed on a color scope. A double projection of the profiles on a conventional pin-writer showed the ischemic regions with count-rate difference between exercise and rest and their localization.

The interpretation of the findings was simplified by assigning the ischemia inthe 3 projections to the anterior wall, the septum and the posterior wall of the left ventricle, respectively. The same areas were compared before and at the end of the drug therapy.

Clinical Features

The patient collective consisted of 31 men and 9 women (average age 56 years) equally distributed in the 2 groups. Coronary angiography in 34 of 40 patients showed 1-vessel disease in 6 patients, 2-vessel disease in 7 patients, 3-vessel disease in 19 patients and coronary artery spasm in 2 patients. Twenty-three patients had a history of coronary artery bypass grafting. Ninety-seven myocardial ischemic areas were found, 47 in group I and 50 in group II (Table I).

Results

In the 40 patients examined in this study, the clinical symptoms after treatment were highly significantly improved, as shown by the reduction in the frequency of angina per week and by the fact that the symptoms recorded at peak individual workload were no longer apparent at the same workloads at the end of the study. Results were similar in the exercise electrocardiogram in which the ST-segment changes at individually equal exercise levels no longer occurred (Tables II and III). In this respect, our results do not differ from the general well-known observations. There was no significant change in the double product of heart rate and blood pressure, although during nifedipine therapy, this value was, on average, increased because of tachycardia.

The scintigraphic study showed a decrease in myocardial ischemia, on average, with both drugs.

In the 97 ischemic areas there were different degrees of reduction or augmentation of ischemia (Fig. 1 and 2).

TABLE I Clinical Features of Patients

	No. of Pts.	Group I ISDN	Group II Nifedipine
No. of Pts.	40	20	20
Men	31	16	15
Women	9	4	5
Mean age (yr)	56 (36–67)	55 (45–66)	57 (36–67)
Severity degree (n = 34)			
1-vessel disease	6	2	4
2-vessel disease	7	1	6
3-vessel disease	19	12	7
Coronary artery spasm	2	2	—
History of aorto-coronary venous bypass surgery	23	14	9
Ischemic myocardial			
Areas	97	47	50
Anterior wall	36	17	19
Septum	29	13	16
Posterior wall	32	17	15

ISDN = isosorbide dinitrate.

TABLE II Results of Isosorbide Dinitrate Treatment

	Before Therapy	After Therapy	Change	% Change
Anginal attacks/ week	12.4 ±12.5	6.3 ±14	−6.1*	−49.1*
ST-segment depression	0.23 ±0.13	0.10 ±0.07	−0.13*	−55*
Double product HR × BP	22,456 ±4,748	21,311 ±4,999	−1,146†	−5.1†
Exercise capacity	320 ±172	320 ±172	0	0
Ischemia (%)	32.3 ±16.4	16.2 ±14.8	−16.1*	−39.7*

* $p < 0.001$; † $p < 0.5$.
BP = blood pressure; HR = heart rate.

TABLE III Results of Nifedipine Treatment

	Before Therapy	After Therapy	Change	% Change
Anginal attacks/ week	10.8 ±9.3	6.1 ±6.0	−4.7*	−43.6*
ST-segment depression	0.16 ±0.16	0.11 ±0.14	−0.05†	−32.1†
Double product HR × BP	19,692 ±4,129	20,420 ±4,541	728	3.7
Exercise capacity	278 ±168	278 ±168	0	0
Ischemia (%)	28.8 ±12.3	20.6 ±1.7	8.2‡	17.2‡

* $p < 0.001$; † $p < 0.5$; ‡ $p < 0.01$.
BP = blood pressure; HR = heart rate.

TABLE IV Myocardial Ischemia Before and After Therapy with Isosorbide Dinitrate Release (120 mg/day)

	No. of Areas	Ischemia Before Therapy (%)	Ischemia After Therapy (%)	% Change
Total patients	47	32.3 ±16.4	16.2* ±14.8	39.7* ±55.2
Significantly reduced	28	37.2 ±16.3	8.6* ±8.3	76.1* ±20.6
Significantly augmentated	5	21.6 ±9.2	33.3* ±8.3	−66.7* ±44.2
Unchanged	14	26.2 ±15.4	25.3 ±16.8	5.01 ±28.2

* $p < 0.001$.

Statistical significances were calculated for each of the ischemic areas. The examined areas were subdivided in accordance with the treatment-induced change into (1) a group with significant improvement, (2) a group with significant worsening and (3) a group with unchanged findings, the latter comprising the statistically nonsignificant improvements and worsening, respectively.

A marked difference was found between both groups in favor of the ISDN-treated group, especially with regard to the number of areas with significantly reduced ischemia—28 (59.5%) vs 20 (40%), and with regard to the unchanged ischemic areas—14 (29.7%) vs 27 (54%)—during nifedipine therapy (Tables IV and V).

Discussion

Most of the studies interpreted by the usual qualitative assessment of the scintigraphic images showed a reduction in myocardial perfusion.[5] These reductions during treatment with both groups of drugs were never described. In our semiquantitative interpretation of ischemia by means of percent-count changes in the ischemic areas, it was possible to judge the scinti-

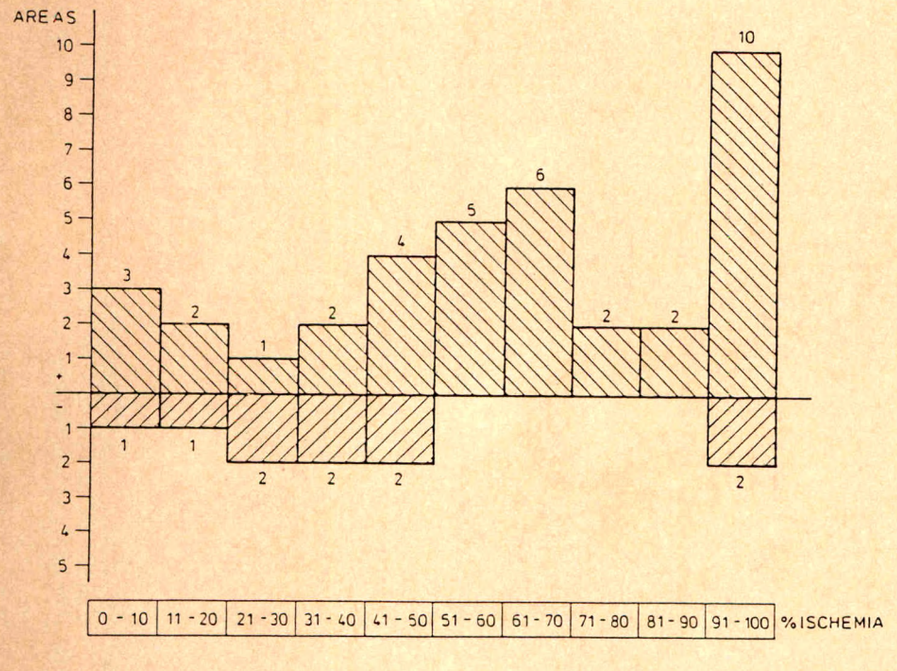

FIGURE 1. Percent ischemic changes of the 47 ischemic areas during therapy with isosorbide dinitrate.

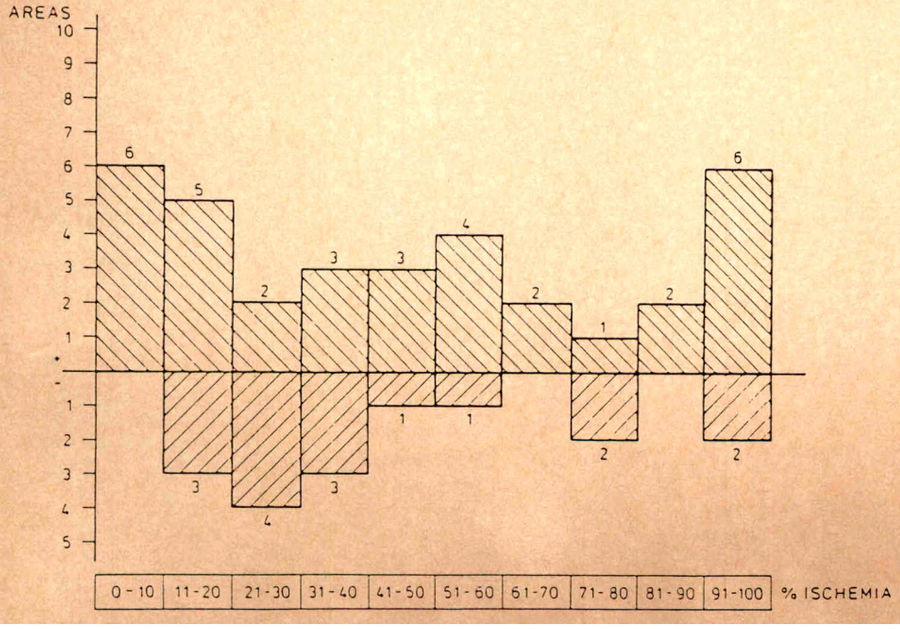

FIGURE 2. Percent ischemic changes of the 50 ischemic areas during therapy with nifedipine.

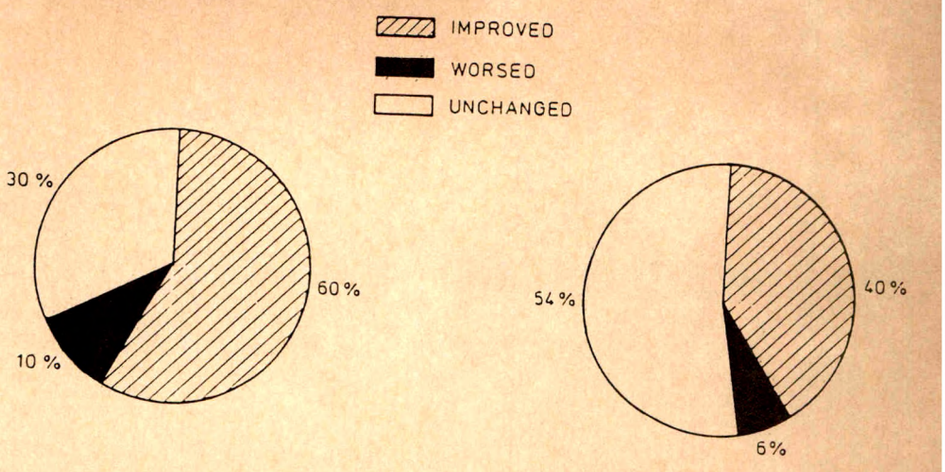

FIGURE 3. ***Left*****, changes in ischemic areas during therapy with isosorbide dinitrate.** ***Right*****, changes in ischemic areas during therapy with nifedipine.**

graphic images more objectively. The calculation of statistical significances for each of the ischemic areas, including a safety factor of 2 sigma, enabled us to assert a clear-cut improvement of worsening of myocardial perfusion after long-term therapy in images taken 1 hour after each drug. The comparison of computerized interpretations that showed significant changes with the usual qualitative interpretation of images was concordant. The statistically calculated nonsignificant reduction and augmentation summarized by us as unchanged findings, could also qualitatively be interpreted as irrelevant changes. In this group, there was a frequent tendency to overrate or underrate findings.

Even though there was a general significant reduction of ischemia in both groups, there was a marked difference in the extent of positive response in ischemic areas in favor of ISDN.

Contrary to the general clinical improvement, the reduction of ischemia was noted scintigraphically only in 60% of the areas during ISDN therapy and only in 40% of the areas during nifedipine therapy. A 90 to 100% disappearance of ischemia was found in 10 areas (22.2%) during ISDN therapy and in 6 areas (12%) during nifedipine therapy. The number of unchanged ischemic areas was 30% after ISDN administration vs 54% after nifedipine. The significant perfusion reduction in 5 areas (10.6%) during ISDN therapy and in 3 areas (6%) during nifedipine therapy can probably be explained by a redistribution of perfusion, or perhaps even by steal effects (Fig. 3). When the clinical relevance of symptomatic improvement was compared with the scintigraphic findings, one may ask whether the persistance of 30% of ischemic areas in group I and 54% of ischemic areas in group II could be interpreted as a change from symptomatic ischemia, recorded before treatment, into an asymptomatic silent ischemia. Holter electrocardiographic recordings showed that patients are unaware of about 80% of all ischemic episodes.[6,7] It is still not fully understood which factors are responsible for this phenomenon. There is still no answer as to whether antianginal therapy leads to an increased endorphin level.[7]

TABLE V Myocardial Ischemia Before and After Therapy with Nifedipine Release (60 mg/day)

	No. of Areas	Ischemia Before Therapy (%)	Ischemia After Therapy (%)	% Change
Total patients	50	28.8 ±12.3	20.6* ±1.7	17.2* ±53.6
Significantly reduced	20	36.2 ±14.1	11.5† ±10.3	69.1† ±24.8
Significantly increased	3	20.5 ±11.3	38.8† ±21.6	−89.1† ±4.9
Unchanged	27	24.2 ±7.8	25.3 ±6.3	−9.3 ±28.3

* $p < 0.01$; † $p < 0.001$.

It should equally be decided whether thallium scintigraphy is perhaps overrated in this respect. However, this procedure appears to be far more sensitive and to yield earlier information on myocardial perfusion than the usual clinical investigative methods. The discovery of silent ischemia is a challenge for us to consider many new questions and aspects of the disease.

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Effects of Isosorbide Dinitrates Intravenously in High Doses Over a Short Period in Anterior Acute Myocardial Infarction

SAMUEL SCLAROVSKY, MD, BORIS STRASBERG, MD, RUBEN F. LEWIN, MD, ALEX ARDITTI, MD, ELIEZER KLAINMAN, MD, and JACOB AGMON, MD

The effects of intravenous isosorbide dinitrate administered in high doses over a short period of time in 17 patients (14 men, 3 women, mean age 67 years) with anterior wall acute myocardial infarction were evaluated. Patients were classified into 2 groups based on the electrocardiographic pattern of acute ischemia. Patients presented with anterior acute myocardial infarction; an electrocardiographic pattern of third-degree ischemia demonstrated a more favorable electrocardiographic and radionuclear angiographic evolution than similar patients who presented with an electrocardiographic pattern of second-degree ischemia.

(Am J Cardiol 1988;61:78E–80E)

The recording of the electrocardiogram during progressive levels of ischemia shows several typical patterns (Fig. 1). The initial phase of ischemia is characterized by the development of a tall and peaked T wave (first-degree ischemia). If the ischemia progresses, then ST-segment elevation (second-degree ischemia) is observed in addition to the tall and peaked T wave. Finally, with maximal ischemia, a further elevation of the ST segment with disappearance of the S wave and an increment in the size of the R wave (third-degree ischemia) is seen.[1,2]

Patients with acute myocardial infarction (AMI) may demonstrate 1 of these 3 degrees of ischemia when admitted to the coronary care unit (if admitted before the development of pathologic Q waves). Each pattern of degree of ischemia has typical evolutionary changes when evolving to AMI (Fig. 2).

The purpose of this study is to evaluate the effects of intravenous isosorbide dinitrate given in high doses over a short period of time on the electrocardiographic (ECG) evolution of patients presenting during the early stages of AMI with initial ECG patterns of second- or third-degree ischemia (Fig. 1 and 2), and to compare the differences between both groups.

From the Israel and Ione Massada Center, Beilinson Medical Center, Petah Tikva, and the Tel Aviv University Sackler School of Medicine, Tel Aviv, Israel.

Address for reprints: Samual Sclarovsky, MD, Massada Center for Heart Diseases, Beilinson Medical Center, Petah

Methods

Inclusion criteria: Patients were admitted to the study when all the following criteria were met: (1) severe chest pain suggestive of AMI of less than 1 hour in duration; (2) an ECG pattern of second- or third-degree ischemia and without pathologic Q waves in the anterior chest leads; (3) no evidence or history of previous transmural (Q wave) anterior wall AMI; (4) a systolic blood pressure of ≥120 mm Hg; and (5) heart rate of no more than 90 beats/min.

Protocol of study: A 3-channel electrocardiogram with fixed precordial leads was recorded every 5 minutes during the first hours and every 15 minutes during the second hour. Radionuclear ventriculography was performed by the first-pass technique during the first 24 hours of admission and 14 days later. Administration of isosorbide dinitrate (50 mg dissolved in 50 ml of 5% dextrose) was started at 166 μg/min and was raised every minute until one of the endpoints was reached. No maximal dose was set. The endpoints of therapy were (1) a reduction in systolic blood pressure to 90 mm Hg, (2) an increment in heart rate >110 beats/min, and (3) a negativization of T waves in the precordial leads or completion of 2 hours of treatment.

Results

Patient characteristics: Seventeen consecutive patients with anterior wall AMI who fulfilled the inclusion criteria were included in the study. There were 14 men and 3 women (ages range from 55 to 74 years [mean 67]). Ten patients had second-grade ischem

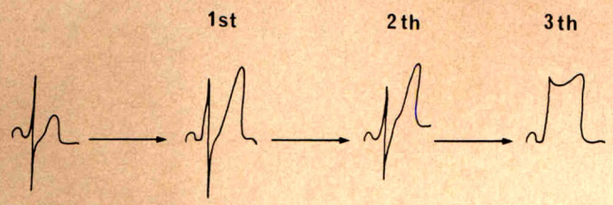

FIGURE 1. Schematic representation of degrees of ischemia. See text for explanation.

(group I), whereas 7 patients had third-degree ischemia (group II). The total dose of isosorbide dinitrate administered during the first hour was 90 ± 25 mg and during the second hour, 80 ± 30 mg.

Electrocardiographic characteristics and comparisons: *Q waves:* In group I, no significant Q waves were observed in the infarcted area within the first 2 hours from the onset of AMI. In group II, pathologic Q waves appeared in all 7 patients within 2 hours.

ST-segment elevation (Fig. 3): In group I, the initial mean level of ST elevation was 9 mm and decreased to

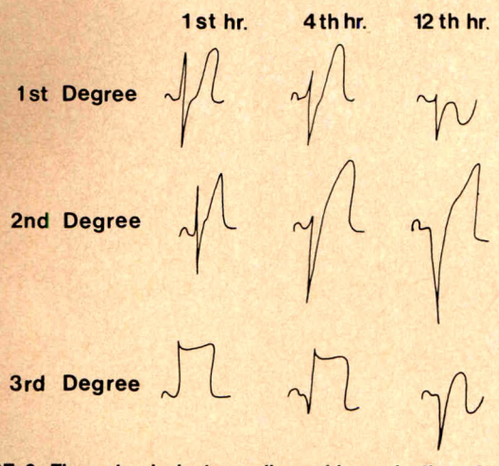

FIGURE 2. The natural electrocardiographic evaluation of acute anterior wall myocardial infarction according to the initial degree of ischemia.

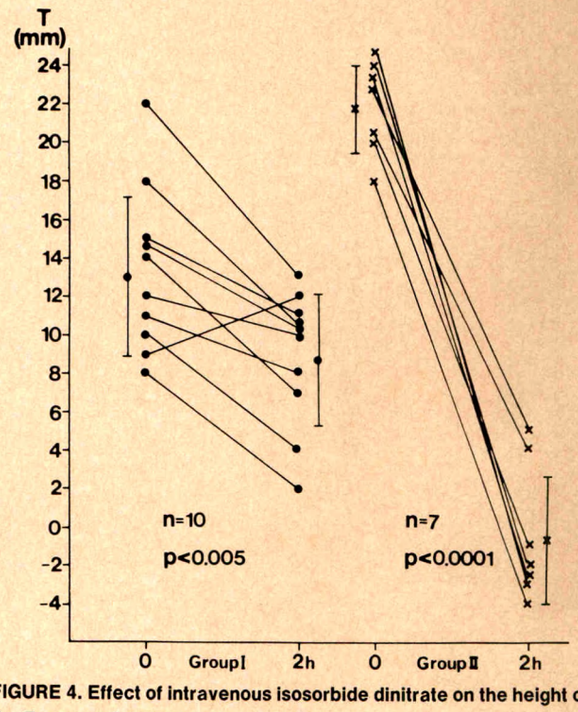

FIGURE 4. Effect of intravenous isosorbide dinitrate on the height of the T waves. See text for explanation.

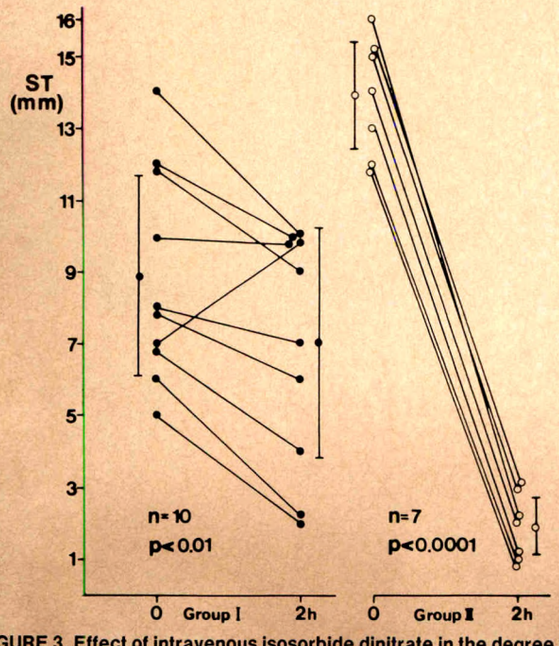

FIGURE 3. Effect of intravenous isosorbide dinitrate in the degree of ST-segment elevation. See text for explanation.

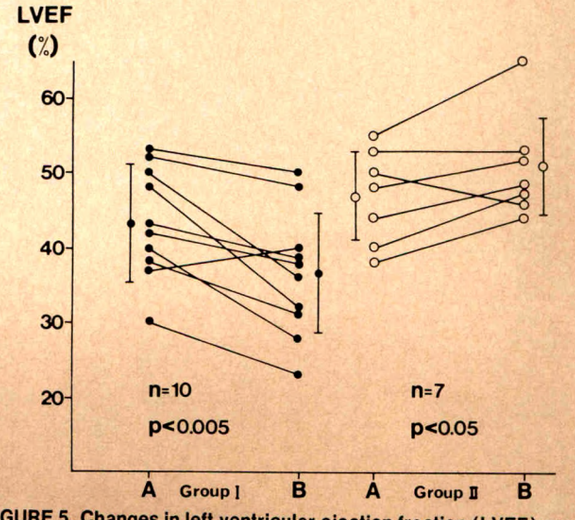

FIGURE 5. Changes in left ventricular ejection fraction (LVEF) over a 2-week period. See text for explanation.

a mean level of 7 mm after 2 hours of treatment ($p < 0.01$). In group II, the initial mean level of ST elevation was 14 mm and decreased to a mean level of 5 mm within 1 hour and to 2 mm within 2 hours of treatment ($p < 0.0001$). Significant differences were found between both groups for these 2 time points: $p < 0.005$ for the first hour and $p < 0.0005$ for the second hour.

T waves (*Fig. 4*): In group I, the initial mean level of the T wave was 13 mm. It remained unchanged after 1 hour of treatment and decreased to 9 mm after 1 hour ($p < 0.005$). In group II, the initial level was 22 mm and decreased to 10.5 mm after 1 hour, and to a negative level of −0.7 mm after 2 hours of treatment. Highly significant differences were observed between T-wave levels in both groups, $p < 0.0001$.

Radionuclear left ventricular ejection fraction (*Fig. 5*): Group I mean initial ejection fraction was 43% and decreased to a mean of 37% after 2 weeks ($p < 0.005$). Group II mean initial ejection fraction was 47% and increased to 53% after 2 weeks ($p < 0.05$). The initial ejection fraction for both groups was similar; however, the second study had statistical differences ($p < 0.005$).

Conclusion

Isosorbide dinitrate, when administered intravenously in high doses over a short period of time, has a beneficial effect on the ECG evolution of patients with anterior wall AMI, when the initial ECG pattern is third-degree ischemia. This treatment can be an alternative mode of therapy for patients with anterior AMI in whom thrombolytic therapy is contraindicated.

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Age-Related Hemodynamic Effects of Intravenous Nitroglycerin for Acute Myocardial Infarction and Left Ventricular Failure

NICCOLO' MARCHIONNI, MD, ADAM SCHNEEWEISS, MD, MAURO DI BARI, MD, LUIGI FERRUCCI, MD, GUYA MOSCHI, MD, BERNARDO SALANI, MD, MARCO PAOLETTI, MD, COSTANZA BURGISSER, MD, and STEFANO FUMAGALLI, MD

Acute hemodynamic effects of intravenous nitroglycerin (NTG) were assessed in 24 patients with acute myocardial infarction and left ventricular failure, and results were compared between 2 groups of different age (group A—65 years or less, n = 12; group B—75 years or more, n = 12). Overall, hemodynamic effects of NTG consisted of an increase in stroke volume index and left ventricular stroke work index (+21 and +23%), coupled with a 16% reduction in systemic vascular resistance, and of a marked decrease in right atrial and pulmonary artery (PA) pressures. The hemodynamic end-point (5 to 10% reduction in mean systemic arterial pressure) used for NTG titration was achieved with a significantly lower dose in group B, in which a greater percent reduction in mean PA and mean PA wedge pressures was also observed. However, because effects of NTG on systemic vascular resistance were similar in groups A and B, it was concluded that the vasodilating action of NTG is maintained in advanced age, as opposed to what has been demonstrated for β-adrenergic agents.

(Am J Cardiol 1988;61:81E–83E)

In aged patients, mortality rates as high as 25 to 50% during acute myocardial infarction (AMI) have been reported,[1,2] and they have been most often attributed to a more frequent occurrence of left ventricular (LV) failure compared with younger patients.[3] Theoretically, the possibilities of a pharmacologic treatment of LV failure are greatly limited in aged patients, as it has been proved that the aging process in itself reduces the responsiveness of the myocardium to positive inotropic agents.[4,5] Vasodilators have been demonstrated to be a valid alternative to inotropic drugs in the treatment of LV failure secondary to AMI. Thus, it would be of interest to verify whether they retain their efficacy at any age. Whereas relaxation of the aorta by isoproterenol decreases with increasing age, such response caused by nitroglycerin (NTG) is not age-dependent in animals.[6]

From the Coronary Care Unit, Institute of Gerontology, University of Florence, Florence, Italy, and the Geriatric Cardiology Research Foundation, Tel-Aviv, Israel.

Address for reprints: Niccolo' Marchionni, MD, Institute of Gerontology, University of Florence, Viale Pieraccini 18, 50139 Florence, Italy.

This study, therefore, has been undertaken in humans to assess the hemodynamic effects of NTG in the elderly with LV failure during AMI and to compare results with those obtained in younger patients.

Methods

Patient selection: To compare groups with markedly dissimilar mean ages, subjects younger than 65 years and older than 75 years with transmural AMI and LV failure—defined as mean pulmonary artery (PA) wedge pressure higher than 15 mm Hg associated with LV stroke work index lower than 35 g·m/m^2—were selected. The following exclusion criteria were used: (1) sustained cardiac arrhythmias, (2) cardiogenic shock, and (3) pretreatment with any drug with known cardiovascular effects. Twenty-four patients were prospectively enrolled into the study: 12 (group A) were aged 65 years or less (mean 59, range 46 to 64), and 12 (group B) were older than 75 years (mean 79, range 75 to 90). The 2 groups did not differ in delay between onset of AMI and the study, prevalence of anterior vs inferior infarct location, and presence of a previous AMI.

Hemodynamic study: A Swan-Ganz catheter was advanced into the PA. A brachial artery was cannulat-

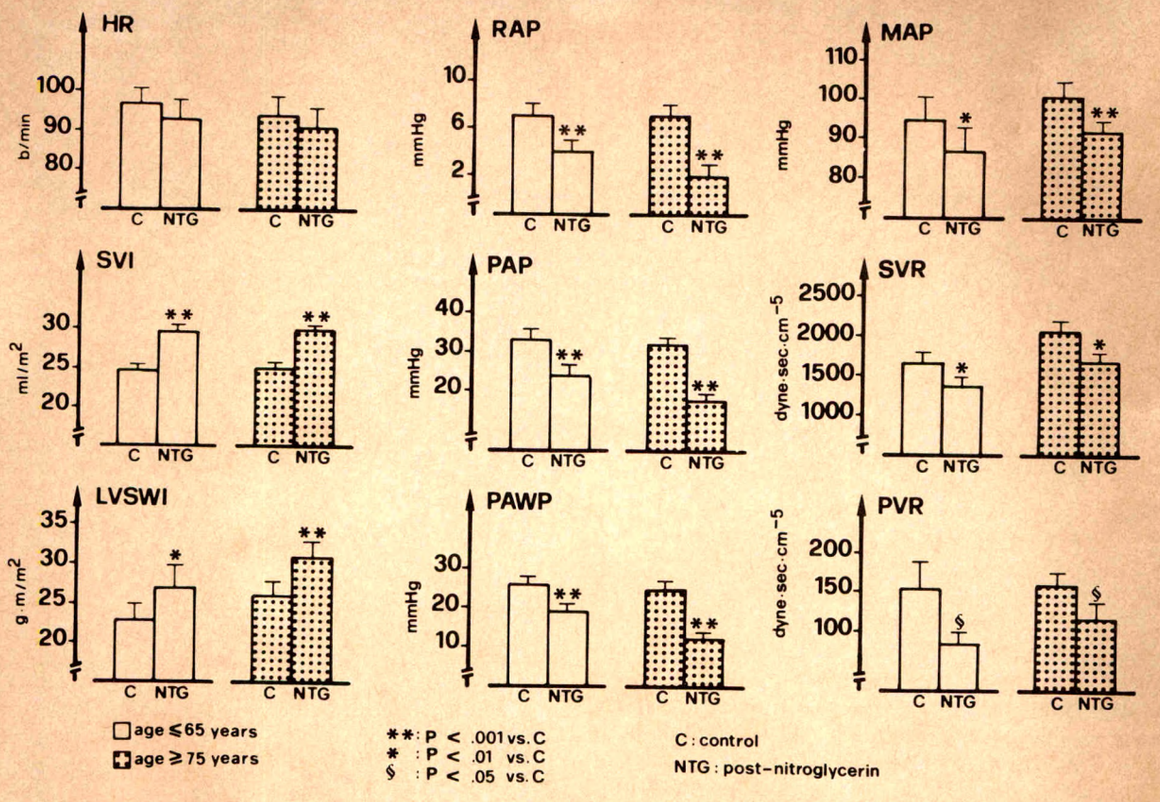

FIGURE 1. Hemodynamic effects of intravenous nitroglycerin (NTG) in young and elderly patients with acute myocardial infarction and left ventricular failure. Hemodynamics after NTG administration were assessed when mean systemic arterial pressure (MAP) was reduced to 5 to 10% of the control (C) value. HR = heart rate; LVSWI = LV stroke work index; PAP = mean PA pressure; PAWP = mean PA wedge pressure; PVR = pulmonary vascular resistance; RAP = mean right atrial pressure; SVI = stroke volume index; SVR = systemic vascular resistance.

ed as well. Pressures were referenced to the midaxillary line, with the patient in the supine position. Cardiac output was measured in triplicate by the thermodilution method. LV stroke work index was calculated as: SVI × (MAP − PAWP) × 0.0136, where SVI = stroke volume index (ml/m^2), MAP = mean systemic arterial pressure (mm Hg), and PAWP = mean PA wedge pressure (mm Hg). Systemic vascular resistance (SVR, dynes s cm^{-5}) and pulmonary vascular resistance (PVR) were calculated as: (MAP − RAP) × 80/CO; (PAP − PAWP) × 80/CO, where RAP = mean right atrial pressure (mm Hg), PAP = mean PA pressure (mm Hg) and CO = cardiac output (liters/min).

Protocol: After basal hemodynamic measurements, NTG was given intravenously by an electric infusion pump at an initial rate of 0.5 μg/kg/min. This dose was increased stepwise by 0.25 μg/kg/min at 5-minute intervals, until mean systemic arterial pressure was lowered 10% from the control level, an endpoint adopted in a previous study of NTG in patients with AMI[7]: at that moment, hemodynamics were reassessed, and time from start of NTG was recorded.

Statistical analysis: Significance of hemodynamic changes within the age groups was tested by 2-tailed *t* test for paired data; Student 2-tailed *t* test for unpaired data was used for comparing the data from the 2 age groups. Differences between percent frequencies were examined by the Fisher exact test. Data are expressed as mean ± standard error of the mean. A p value <0.05 was considered significant.

Results

Hemodynamic findings: A marked improvement after NTG infusion occurred in both groups (Fig. 1), as indicated by a relevant increase in stroke volume index and LV stroke work index, by a slight (−16%) but significant reduction in systemic vascular resistance and by a sharp decrease in right atrial and PA pressures. Reduction in mean systemic arterial pressure attained statistical significance in both groups, while heart rate was insignificantly reduced.

Comparison of the effects of nitroglycerin in groups A and B: Control hemodynamics were similar in the 2 groups. The selected hemodynamic endpoint was reached after a lower dose of NTG and in a shorter time in group B (0.7 ± 0.1 vs 1.7 ± 0.3 μg/kg/min, p <0.02; 17 ± 1 vs 33 ± 5 minutes, p <0.01). To ascertain whether some difference existed between young and elderly patients in their response to NTG, percent changes observed in group A and B were com-

pared (Table I). Changes in stroke volume index, LV stroke work index and systemic vascular resistance were almost identical in the 2 groups. Elderly patients showed a significantly greater reduction in mean PA and mean PA wedge pressures.

Mortality rates: Mortality rate was higher in group B than in group A (50 vs 17%), but such a difference did not attain statistical significance ($p = 0.09$). Two patients in group A and 3 in group B died from pulmonary edema. Three other elderly patients died from cardiogenic shock (n = 1) and from pulmonary thromboembolism (n = 2).

Discussion

Hemodynamic effects of intravenous NTG in patients with AMI with secondary LV failure are well established,[8] and consist of predominant venodilation associated with minor dilation of the arterial bed. Similarly, a marked reduction in right atrial, mean PA and mean PA wedge pressures (−70, −35 and −40%, respectively), coupled with a 16% decrease in systemic vascular resistance, was seen in all 24 patients.

Previous clinical trials[7,8] of NTG in AMI did not mention any comparison between young and elderly patients; moreover, an advanced age was considered as an exclusion criterion in some of those studies. In the present study, the same hemodynamic endpoint was achieved in group B, with a smaller amount of NTG than in group A. This may be the consequence either of increased sensitivity to NTG or of altered pharmacokinetics in the elderly. Because aging does not modify the in vitro sensitivity of aortic smooth muscle to NTG,[6] it is more likely that reduced metabolism was the reason for the lower effective dose in aged patients. This hypothesis is supported by a preclinical study[9] demonstrating a prolonged NTG half-life in older animals, secondary to reduced hepatic microsomal enzymatic activity.

The effects of NTG on venous return were more pronounced in elderly than in younger patients, as indicated by a more relevant reduction in right atrial and PA pressures. In our study (patients with similar changes in cardiac output, studied at rest in a recumbent, fixed position), venous return should depend only on venous tone and on the circulating blood volume. Thus, the reason for an age-dependent effect of NTG on parameters that are a function of venous return should either be a quantitatively different action on the venous vascular bed of young and elderly subjects or an age-related decrease in the circulating blood volume. Because NTG induced identical dilation in the portal veins of young and senescent animals,[6] the drug should have exerted similar effects on venous tone in groups A and B. An age-related decrease in extracellular fluids and in plasma volume have been indicated as a cause of the frequent untoward reactions to antihypertensive agents in the elderly.[10] Thus, a diminished plasma volume may have been the origin of the greater reduction in right atrial and PA pressures observed in group B than in group A.

TABLE I Percent Changes in Hemodynamic Parameters After Intravenous Nitroglycerin in Patients Aged 65 Years or Less (Group A) and 75 Years or More (Group B)

Variable (%)	Group A	Group B	p Value
HR	−4 ± 2	−3 ± 2	NS
SVI	22 ± 5	21 ± 5	NS
LVSWI	22 ± 6	25 ± 5	NS
MAP	−7 ± 2	−8 ± 2	NS
SVR	−16 ± 3	−16 ± 4	NS
RAP	−58 ± 7	−82 ± 11	NS
PAP	−28 ± 3	−42 ± 5	<0.02
PAWP	−29 ± 4	−51 ± 5	<0.005
PVR	−23 ± 10	−24 ± 11	NS

Abbreviations as in Figure 1.
NS = not significant.

However, we demonstrated that the vasodilating properties of NTG are preserved in elderly patients, in whom this drug is thereby a powerful aid in the treatment of LV failure secondary to AMI. In a recent randomized prospective trial,[7] NTG did not reduce immediate and 3-month mortality rates after AMI; similarly, despite relevant hemodynamic improvement, the prognosis of elderly patients in our study remained severe.

Further investigation is necessary to confirm age-dependent changes in NTG pharmacokinetics in humans. Nevertheless, since comparable hemodynamic effects were obtained after smaller amounts of NTG, the present study indicates that lower doses of NTG should be recommended in the elderly, in order to prevent excessive hypotension, particularly in patients with nearly normal pulmonary pressures.

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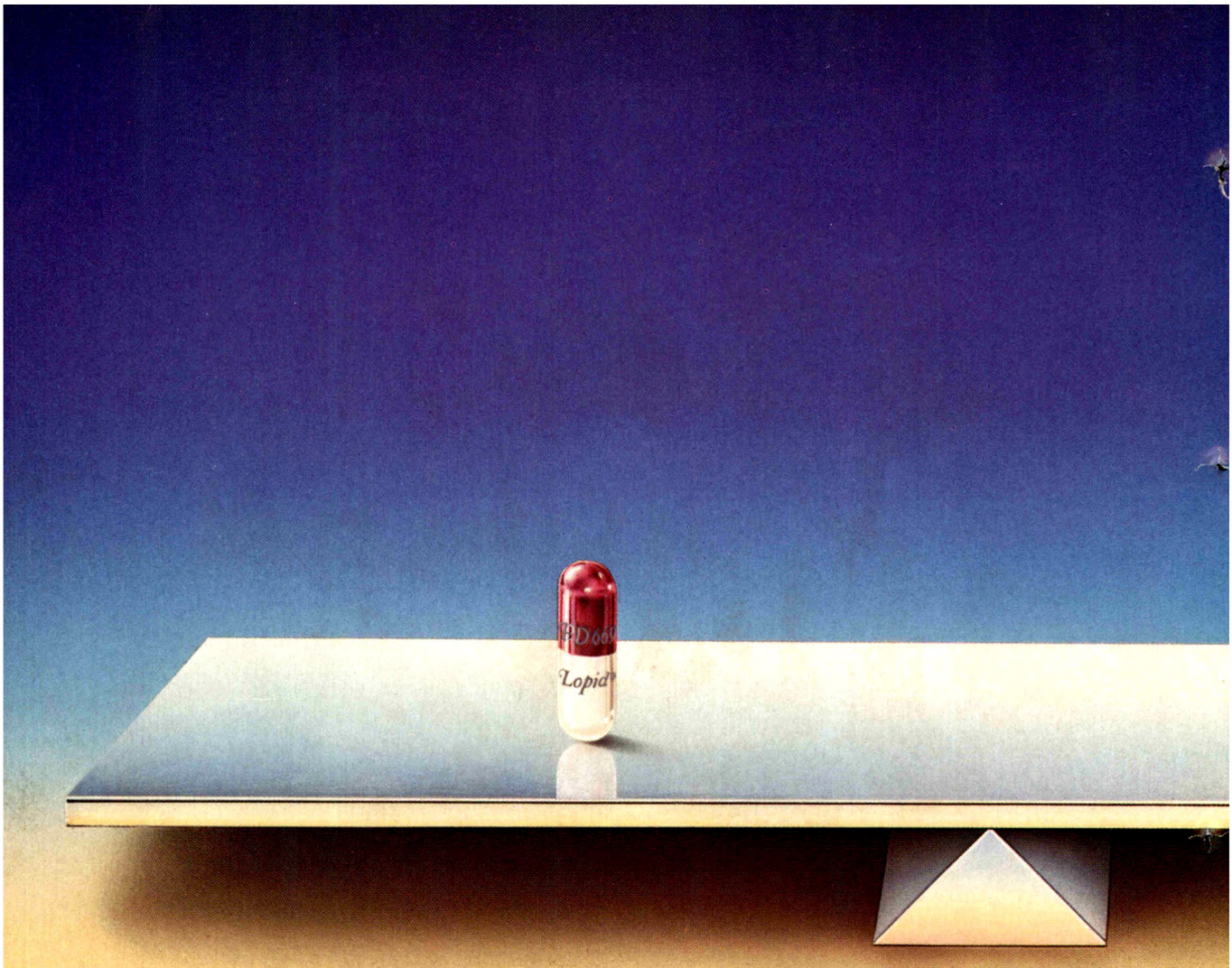

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CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. It has been reported that LOPID may increase levels of high density lipoprotein (HDL) subfractions, HDL_2 and HDL_3 as well as apolipoproteins AI and AII. Epidemiological studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease. It is not yet known whether pharmacological interventions designed to raise HDL-cholesterol alter morbidity or mortality due to coronary heart disease.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID inhibits synthesis and increases clearance of VLDL carrier apolipoprotein B, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, mostly as the glucuronide conjugate, with less than 2% excreted as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO: HDL Cholesterol / Total Cholesterol
		Total	VLDL	LDL	HDL	
IIa	−44%	−4.2%	−44.3%	−5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	−6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. The initial treatment for hyperlipidemia is dietary therapy specific for the type of hyperlipoproteinemia. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV or type V hyperlipoproteinemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk. LOPID has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of gemfibrozil-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID (gemfibrozil capsules, USP) administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis – LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy** – Before instituting LOPID therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy** – Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Impairment of Fertility** – Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

4. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

5. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

6. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

7. **Liver Function** – Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

8. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria

Central Nervous System: headache, dizziness, blurred vision

Musculoskeletal: painful extremities

Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:

Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia

Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints, myositis

Central Nervous System: vertigo, insomnia, paresthesia, tinnitus

Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)

Miscellaneous: fatigue, malaise, syncope, alopecia

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

Caution – Federal law prohibits dispensing without prescription.

February 1987 0669G017

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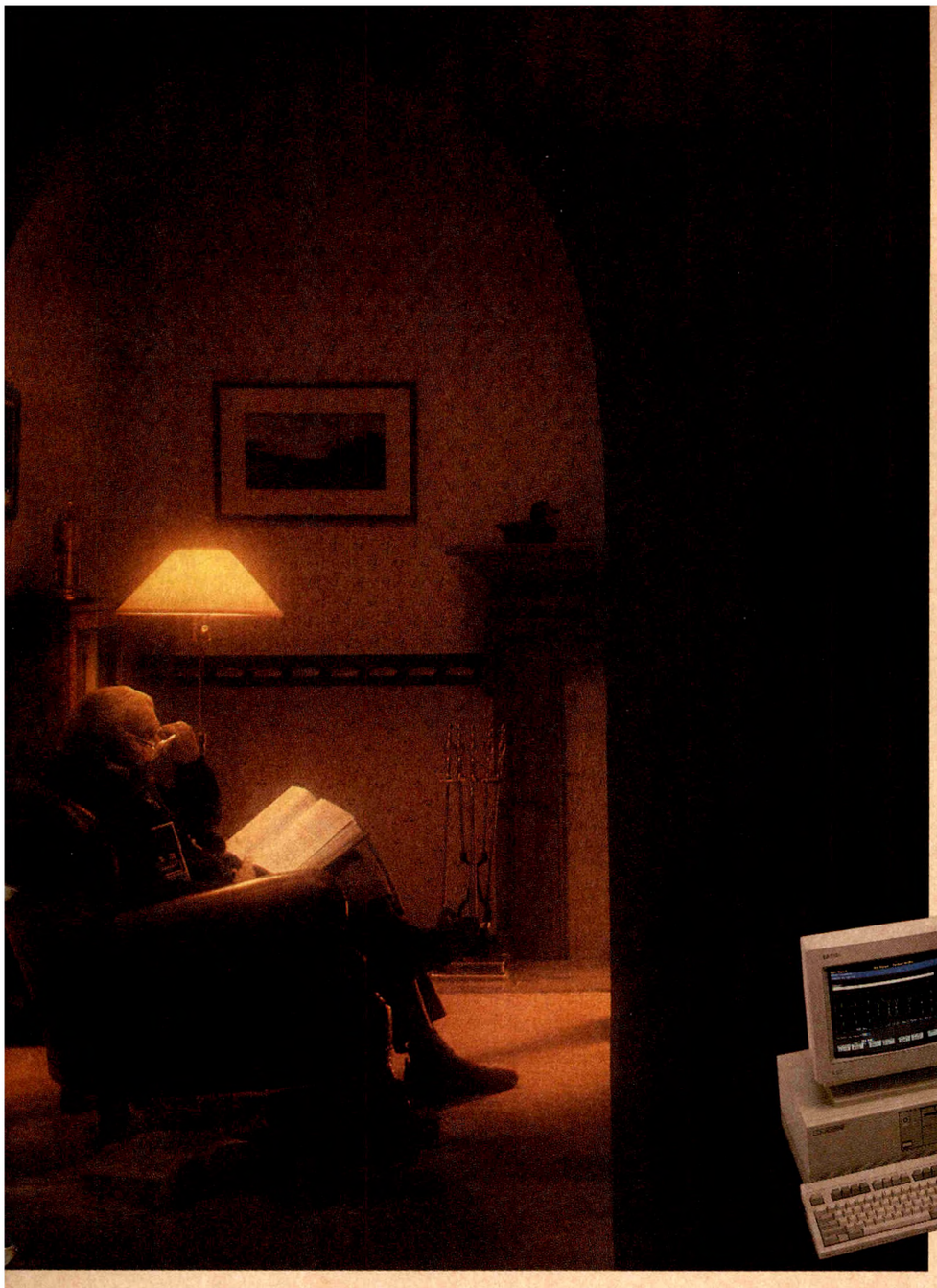

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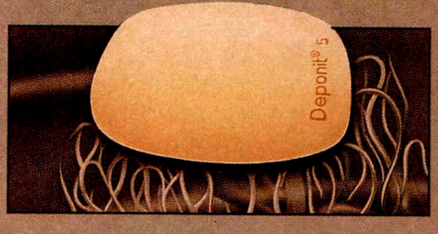

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*"Gradient-charged™" refers to the differential concentration of free and bound NTG, which results in continuous transport and controlled release of free drug at the skin surface.

†Effectiveness of this product has not been established pending final evaluation by FDA (see prescribing information).

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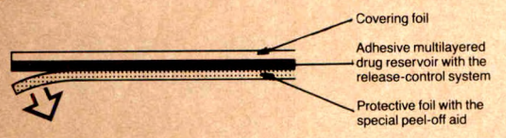
See important information on next page.

WYETH AYERST™

Wyeth-Ayerst®
Deponit®
(nitroglycerin transdermal delivery system)
5 mg/24 hours, 10 mg/24 hours

Description
Deponit® is a unique nitroglycerin-containing transdermal delivery system. A multilayered self-adhesive film, the system contains nitroglycerin in a matrix composed of lactose, plasticizer, medical adhesive, polyisobutylene, and aluminized plastic for controlled release of the active agent through the skin into the systemic circulation. For the 24 hours during which the system is applied to the intact skin, its technology is intended to deliver an accurate dosage with no premature release of the nitroglycerin or undesired accumulation on the skin. Nitroglycerin (glyceryl trinitrate) is a vasodilator for the relief and prevention of anginal attacks.
Deponit® is available in two strengths which release either 5 mg or 10 mg of nitroglycerin during a 24-hour period. The 5 mg/24 hr system has a 16 cm^2 releasing surface and contains 16 mg nitroglycerin. The 10 mg/24 hr system has a 32 cm^2 releasing surface and contains 32 mg nitroglycerin.
The Deponit® system is approximately 0.3 mm thick, insoluble in water, and, as illustrated below, consists of two main elements:
1. A flexible, flesh-colored waterproof covering foil.
2. A multilayered adhesive film that constitutes simultaneously the drug reservoir and the release-control system.



The system is protected by an aluminum foil which has a patented S-shaped opening to facilitate its removal prior to use of the system.

Clinical Pharmacology
When the Deponit® system is applied to the skin, nitroglycerin is continuously released for absorption directly into the systemic circulation. Thus, active drug reaches the target organs (heart, extremities) before deactivation by the liver. Nitroglycerin is a smooth-muscle relaxant with vascular effects manifested predominantly by venous dilatation and pooling. The major beneficial effect of nitroglycerin in angina pectoris is a reduction in myocardial oxygen consumption, secondary to vascular smooth-muscle relaxation with resultant reduction in cardiac preload and afterload. In recent years there has been increasing recognition of a direct vasodilator effect of nitroglycerin on the coronary vessels.
In a bioavailability study using healthy volunteers,[1] transdermal absorption of nitroglycerin from the Deponit® system achieved steady-state venous plasma levels and maintained these levels for 24 hours. Detectable plasma levels were attained within 30 minutes after application of the system and were still detectable 30 minutes after removal of the system.
The amount of nitroglycerin released (5 mg/24 hr or 10 mg/24 hr) represents the mean release rate of nitroglycerin from the system as determined from healthy volunteers, and hence, the amount potentially available through the skin. Absorption will vary among individuals. Precise definition of "therapeutic plasma level" is not known at this time.

Indications and Usage
This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

Contraindications
Nitroglycerin is contraindicated in patients known to be intolerant of organic nitrate drugs and in patients with marked anemia.

Warnings
In patients with acute myocardial infarction or congestive heart failure, nitroglycerin should be used under careful clinical and/or hemodynamic monitoring.
In terminating treatment of patients with angina, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent the sudden withdrawal reactions which are characteristic of vasodilators in the nitroglycerin class.
Transdermal nitroglycerin systems should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may enhance the possibility of arcing, a phenomenon associated with the use of defibrillators.

Precautions
Symptoms of hypotension, such as faintness, weakness, or dizziness, particularly orthostatic hypotension, may be due to overdosage. When these symptoms occur, the dosage should be reduced or use of the product discontinued.
Deponit® is not intended for use in treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitrates may be necessary.
PREGNANCY
Pregnancy Category C. Animal reproduction studies have not been conducted with nitroglycerin. It is not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.
NURSING MOTHERS
It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when the preparation is administered to a nursing woman.

Adverse Reactions
Transient headache is the most common side effect, especially when higher doses of the drug are used. These headaches should be treated with mild analgesics while Deponit® therapy is continued. When such headaches are unresponsive to treatment, the dosage should be reduced or use of the product discontinued.
Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis these symptoms are attributable to the known pharmacologic effects of nitroglycerin, but may be symptoms of overdosage. When they persist, the Deponit® dose should be reduced or use of the product discontinued.

Dosage and Administration
Deponit® can be applied as a single system or as multiples, depending upon the clinical requirements. Dosage should be titrated to achieve the optimal therapeutic effect by monitoring clinical response, side effects, heart rate, and the effect of therapy upon blood pressure.
Deponit® should be removed from the single-unit package just prior to use. The protective aluminum precut S-shaped foil is removed according to the "Patient Instructions," and the system is applied with a firm pressure on a convenient skin site, preferably on the chest, inner side of the upper arm, or shoulders. Deponit® should not be applied to the distal parts of extremities.
Each system is designed to remain in place for 24 hours; however, the treatment site should be changed daily to minimize skin irritation and should be intact, clean, and dry. If necessary, hair may be removed by clipping.
Therapy should be initiated with application of a single Deponit® system, delivering 5 mg every 24 hours. Response in terms of satisfactory control of anginal symptoms without adverse effects should be evaluated to determine the optimal dose. Some patients may require adjustment of dosage to provide a better clinical response. This can be achieved by removing the system delivering 5 mg/24 hours, and applying a larger system delivering 10 mg/24 hours or a multiple of either system, depending on the dose required to achieve the desired effect.
After 24 hours, the system should be removed and discarded. Because no adhesive residue remains on the skin, there is no need to use a solvent.

Storage Conditions
Store at room temperature not above 25°C (77°F). Do not refrigerate.

Patient Instructions for Application
A leaflet describing use of Deponit® is provided with each package.

How Supplied
Deponit® (nitroglycerin transdermal delivery system), Wyeth-Ayerst®, is packaged in cartons containing unit doses of 30 flesh-colored systems on aluminum backings. See table below.

Nitroglycerin released *in vivo*	Total drug content/ system	System size	Carton size
5 mg/24 hrs	16 mg	16 cm^2	30 Systems **(NDC 0008-4195-01)**
10 mg/24 hrs	32 mg	32 cm^2	30 Systems **(NDC 0008-4196-01)**

Caution: Federal law prohibits dispensing without prescription.

Reference
1. Data on file: Wyeth-Ayerst Laboratories Inc., Philadelphia, PA 19101.

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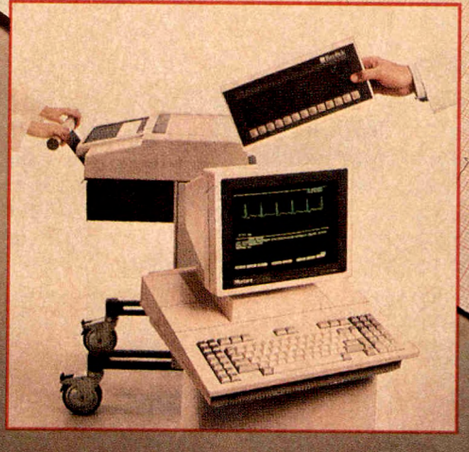

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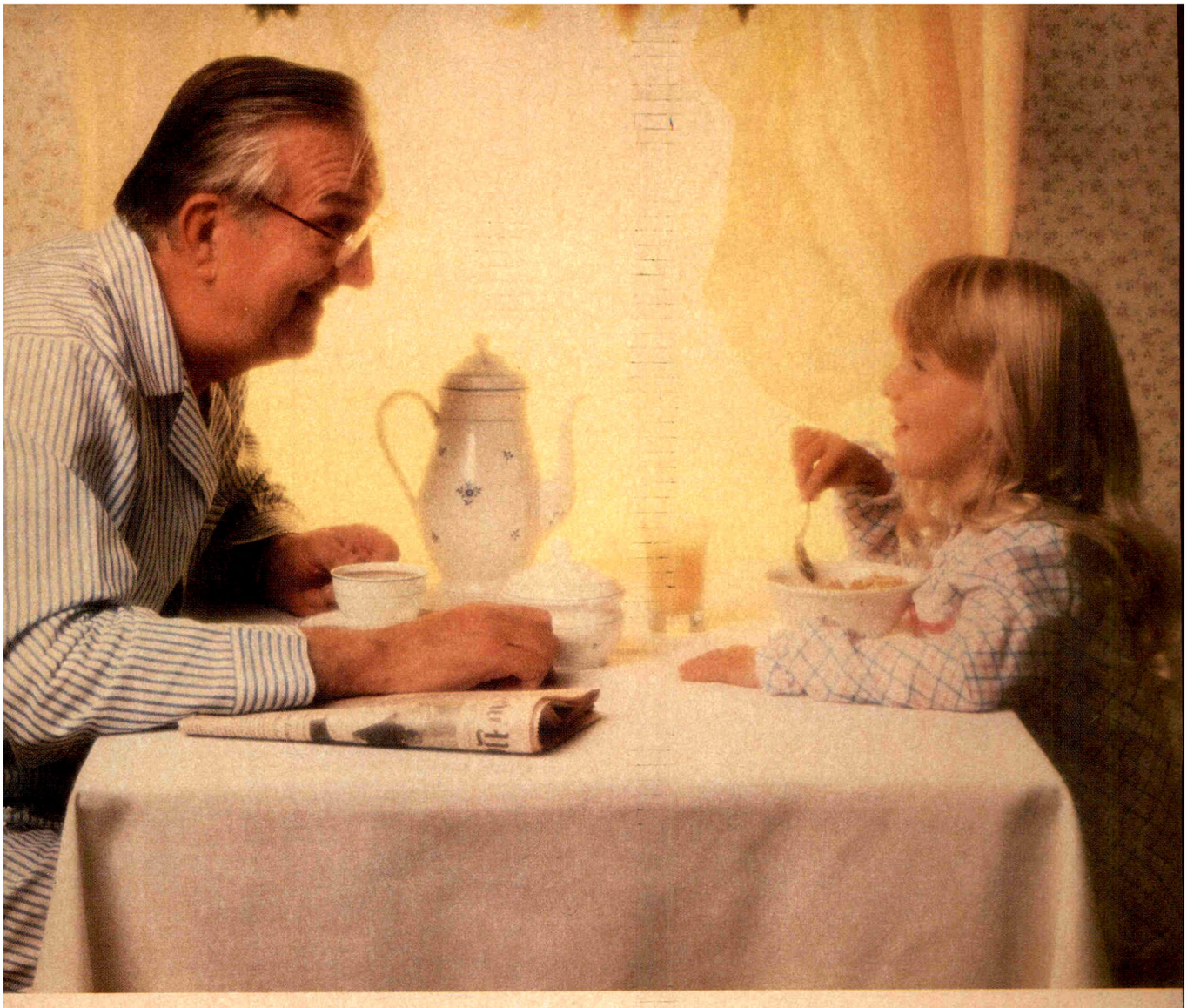

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CORGARD® TABLETS
Nadolol Tablets USP

DESCRIPTION: CORGARD (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal—Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2- week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery—Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia—Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis—Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function—Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients—Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions—Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)—hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (e.g., reserpine)—additive effect; monitor closely for hypotension and/or excessive bradycardia.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In 1 to 2 year oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C—In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia and associated symptoms.

Nursing Mothers—Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular—Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**—Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**—Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**—Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**—reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**—mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**—agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**—fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**—pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm—Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE—For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg qd; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg qd (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg qd; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg qd (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 20, 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100. The 40 mg, 80 mg, and 120 mg tablets are available in bottles of 1000 tablets. The 20 mg, 40 mg, and 80 mg tablets are also available in Unimatic® unit-dose packs of 100 tablets.

(J4-156)

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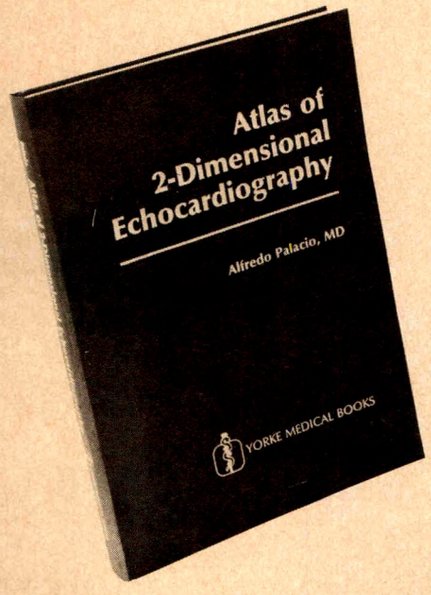

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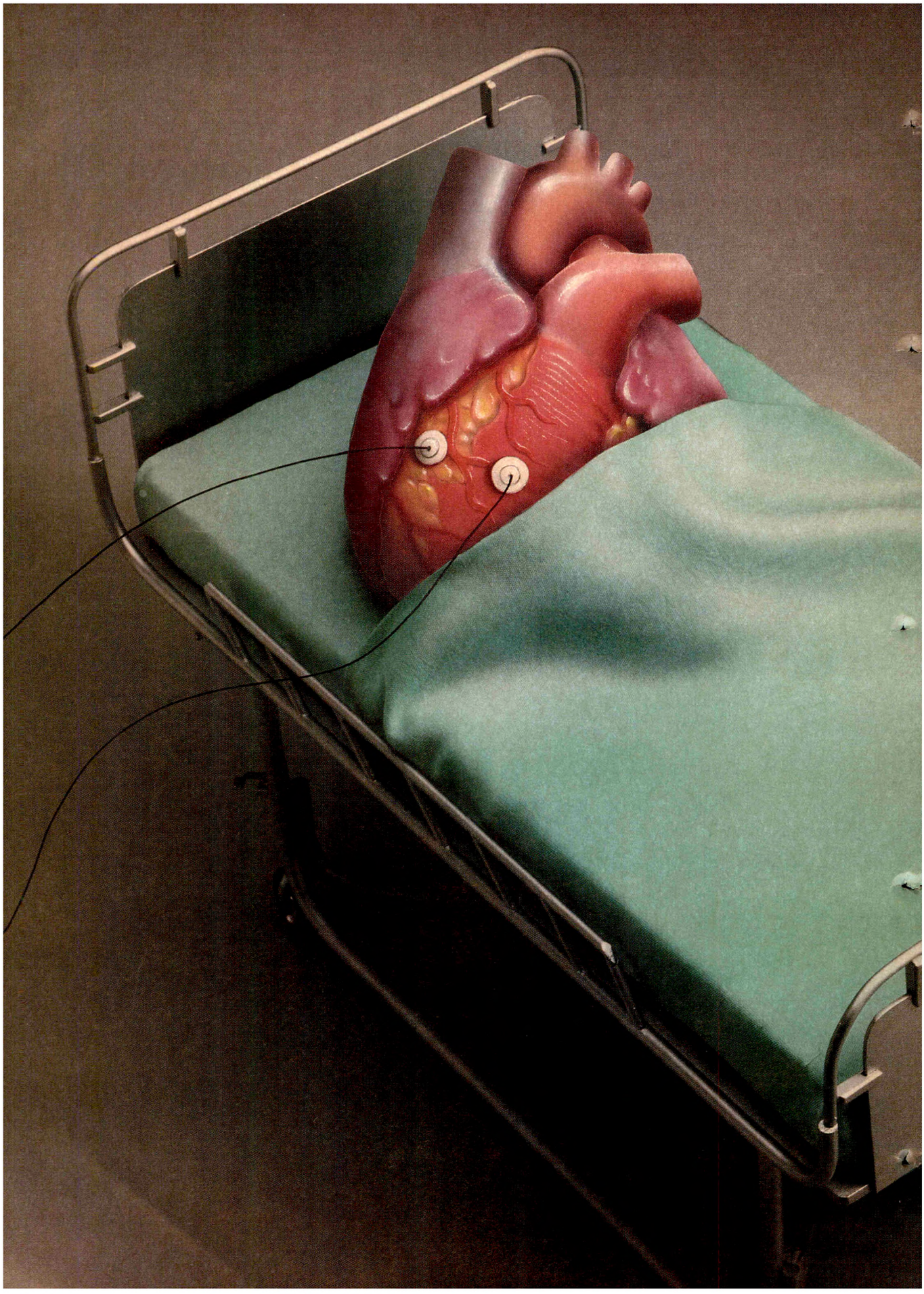

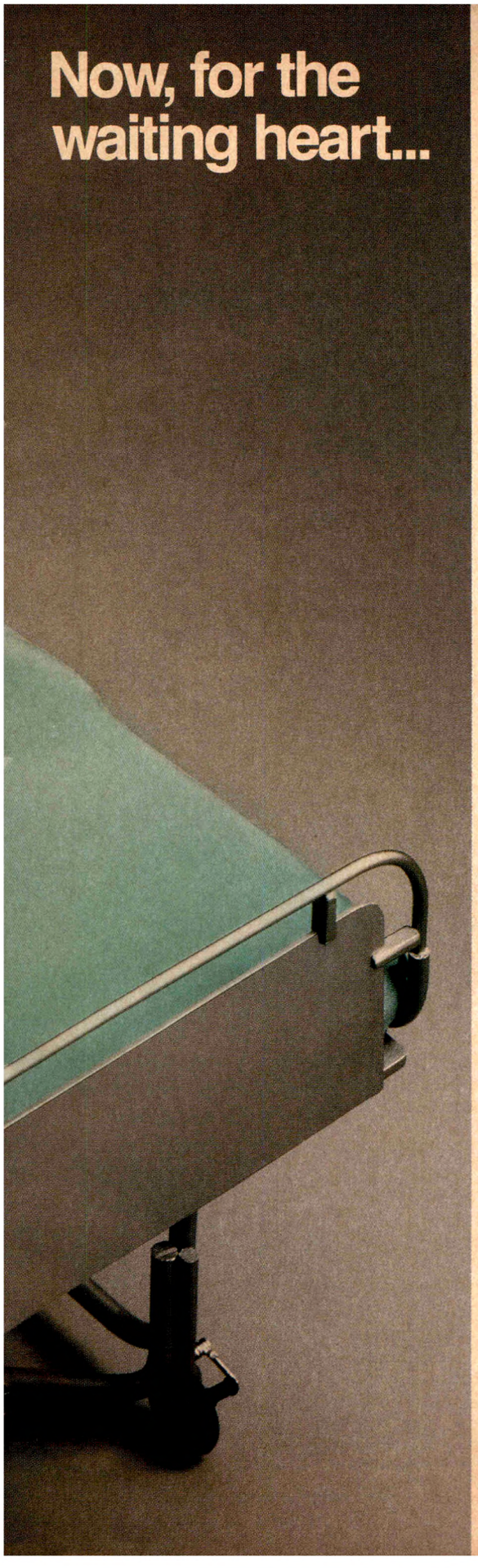

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CORONARY ARTERY DISEASE

677 **Determinants and Protective Potential of Coronary Arterial Collaterals as Assessed by an Angioplasty Model**

K. Peter Rentrop, John C. Thornton, Frederick Feit, and Mark Van Buskirk

Two indexes of collateral blood flow, distal coronary occlusion pressure/aortic pressure and angiographic collateral class, were determined during elective angioplasty and correlated with anatomic and clinical variables in 36 patients with normal left ventricular function. A reduction in luminal diameter by >70% predicted collaterals with 100% specificity and 85% sensitivity. Lesion severity correlated with both collaterals indexes, suggesting a quantitative relation between lesion severity and collateral development beyond a threshold value of 70% stenosis. Left ventricular ejection fraction during ischemia caused by balloon occlusion was found to be primarily determined by lesion location; however, collateral flow modified the ejection fraction significantly. A model predicting the hemodynamic and clinical consequences of abrupt coronary closure based on lesion location and severity was developed and subsequently tested in another group of 23 patients who experienced coronary occlusion as a complication of angioplasty. The data suggest an inverse relation between lesion severity and the extent of functional as well as clinical consequences of abrupt coronary closure.

685 **Usefulness of Serial Radionuclide Monitoring During Graded Nitroglycerin Infusion for Unstable Angina Pectoris for Determining Left Ventricular Function and Individualized Therapeutic Dose**

Warren M. Breisblatt, Nestor A. Vita, Marcos Armuchastegui, Lawrence S. Cohen, and Barry L. Zaret

Using serial invasive hemodynamics in concert with noninvasive radionuclide monitoring of left ventricular function, 20 patients with unstable angina were evaluated during incremental infusion of intravenous nitroglycerin. Seventeen of 20 patients demonstrated a favorable hemodynamic response. In general, there was excellent agreement between hemodynamic and noninvasive radionuclide measurements. Cardiac output improved by 29% (mean 4.7 ± 1.2 to 6.0 ± 1.3), left ventricular ejection fraction increased an average of 0.11 (0.39 ± 0.14 to 0.50 ± 0.16) and diastolic function as assessed by peak-filling rate improved from 1.80 ± 0.60 end-diastolic volume/s to 2.7 ± 0.90. The dose of nitroglycerin necessary to produce maximal hemodynamic benefit was variable. In 7 patients, nitroglycerin caused adverse hemodynamics, which corrected with intravenous fluids, allowing continued administration of intravenous nitroglycerin. Peak systolic pressure–end-systolic volume relations were assessed to define possible changes in left ventricular contractility. In 12 patients, this relation was linear, suggesting altered loading as nitroglycerin's mechanism of action. In 3 patients a downward and rightward shift of the systolic relation was seen, suggesting that significant underloading with nitroglycerin was associated with depressed contractility.

Continued on page A24

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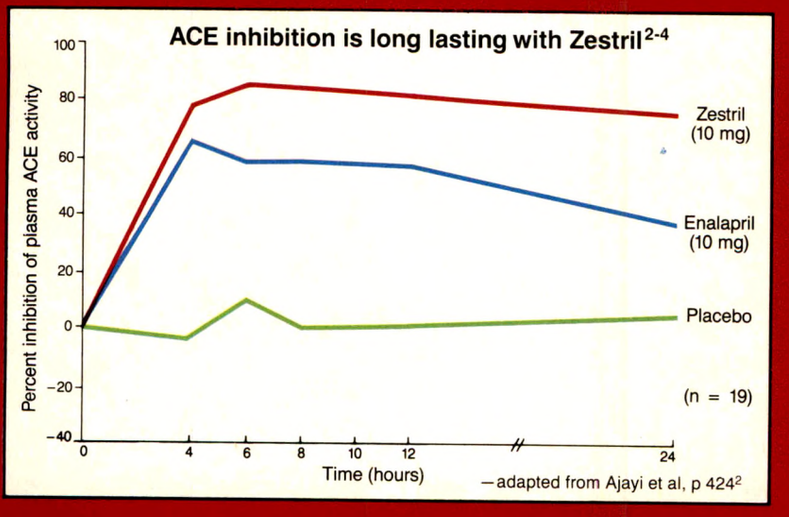

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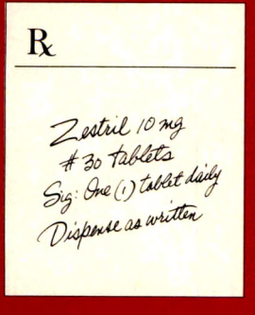

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*The antihypertensive effect may diminish at the end of the dosing interval.

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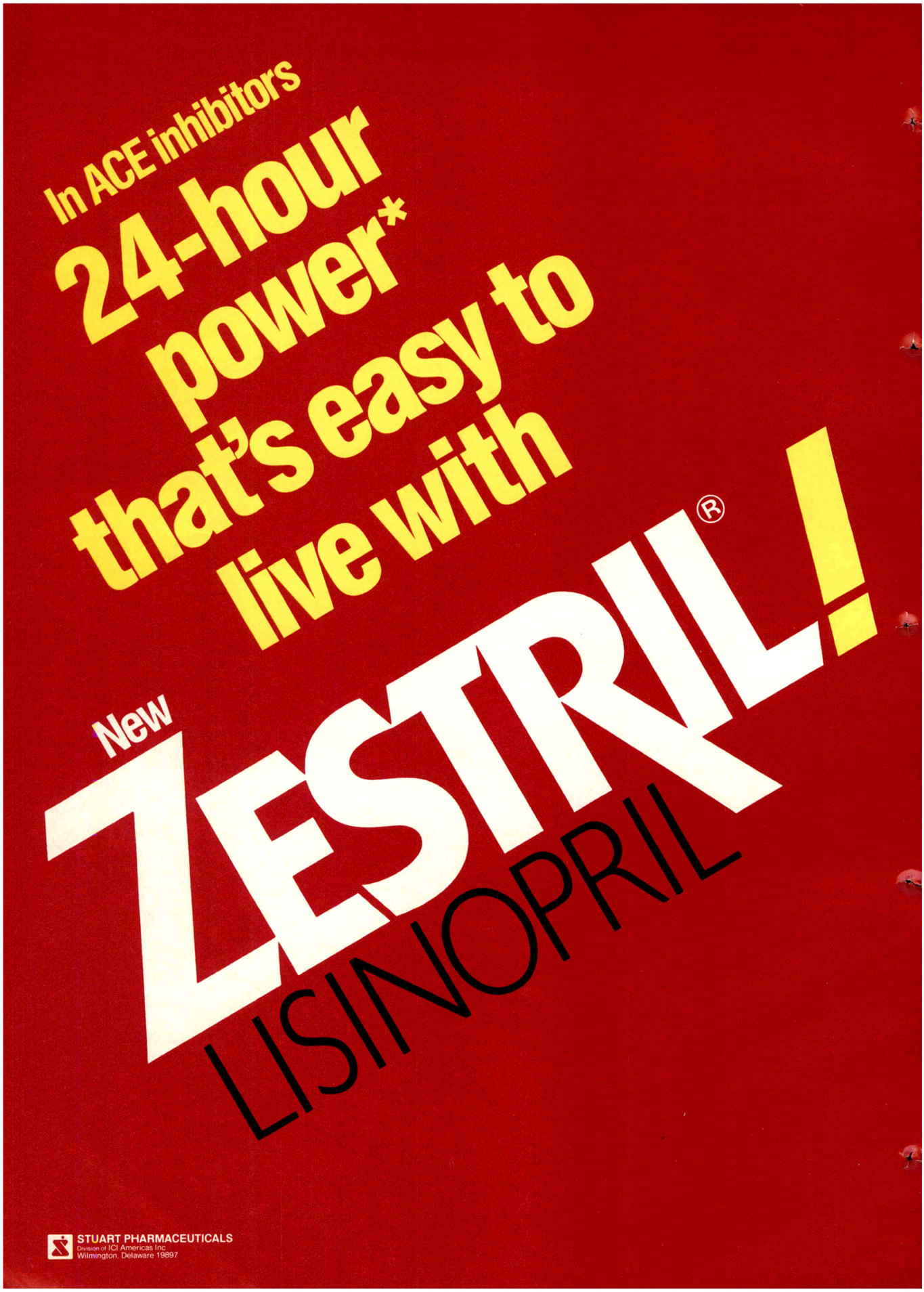
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Zestril: 24-hour blood pressure control without liver metabolism

Zestril provides 24-hour control. Zestril is not metabolized by the liver.[7] It does not require bioactivation[7]—as needed with prodrugs such as enalapril.**[5,7] Zestril is absorbed as an active drug.[1] Absorption is unaffected by food.[8]

Zestril: 24-hour blood pressure control that's well tolerated

Zestril achieves 24-hour control with a low incidence of side effects. Rash and/or taste disturbance are rarely seen with Zestril. In Zestril clinical trials, the most frequently reported side effects were as follows:

Side Effects	Zestril (n = 2,003‡)	—	Placebo (n = 207)
Dizziness	6.3%	—	1.9%
Headache	5.3%	—	1.9%
Fatigue	3.3%	—	1.0%
Diarrhea	3.2%	—	2.4%
Upper respiratory symptoms	3.0%	—	0.0%
Cough	2.9%	—	1.0%

‡Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

- Only 6% of patients discontinued therapy in controlled clinical trials.
- Symptomatic hypotension occurs infrequently (0.8%) in patients with normal renal function but is a possible consequence in salt/volume-depleted persons such as those treated vigorously with diuretics.
- Evaluation of the hypertensive patient should always include assessment of renal function. (See Dosage and Administration.)
- Angioedema has been reported with ACE inhibitors, including Zestril. (See Warnings.)

Zestril dosage in hypertension
Starting dose is 10 mg once a day. Usual dosage range for maintenance: 20 to 40 mg per day, administered in a single daily dose.

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LISINOPRIL

**Clinical significance has not been determined in hypertensive patients.

*The antihypertensive effect may diminish at the end of the dosing interval.

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INDICATIONS AND USAGE. Zestril is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents. In using Zestril, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that Zestril does not have a similar risk. (See WARNINGS.) **CONTRAINDICATIONS.** Zestril is contraindicated in patients who are hypersensitive to this product. **WARNINGS. Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including Zestril. In such cases, Zestril should be promptly discontinued, and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, eg, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered. (See ADVERSE REACTIONS.) Hypotension:** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of use with Zestril in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of Zestril and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. **Neutropenia/Agranulocytosis:** Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of Zestril are insufficient to show that Zestril does not cause agranulocytosis at similar rates. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered. **PRECAUTIONS. General. Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including Zestril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of Zestril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when Zestril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of Zestril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.) Hyperkalemia:** In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with Zestril. (See Drug Interactions.) **Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Zestril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion. **Information for Patients. Angioedema:** Angioedema, including laryngeal edema, may occur especially following the first dose of Zestril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician. **Symptomatic Hypotension:** Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician. **Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician. **Neutropenia:** Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which may be a sign of neutropenia. **NOTE:** As with many other drugs, certain advice to patients being treated with Zestril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. **Drug Interactions. Hypotension – Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Zestril. The possibility of hypotensive effects with Zestril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Zestril. If it is necessary to continue the diuretic, initiate therapy with Zestril at a dose of 5 mg daily, and provide medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving Zestril, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.) **Indomethacin:** In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of Zestril alone were compared to Zestril given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant. **Other Agents:** Zestril has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when Zestril was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of Zestril. **Agents Increasing Serum Potassium:** Zestril attenuates potassium loss caused by thiazide-type diuretics. Use of Zestril with potassium-sparing diuretics (eg, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 times* the maximum recommended daily human dose) or when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). *Based on patient weight of 50 Kg. Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow. There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. **Pregnancy. Pregnancy Category C:** Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1,000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1,000 mg/kg this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation. Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man. Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at a dose of lisinopril at 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). By whole body autoradiography, radioactivity was found in the placenta following administration of labeled lisinopril to pregnant rats, but none was found in the fetuses. There are no adequate and well-controlled studies in pregnant women. Zestril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. It is not known whether this drug is excreted in human milk.

ZESTRIL® (lisinopril)

Because many drugs are excreted in human milk, caution should be exercised when Zestril is given to a nursing mother. **Pediatric Use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS.** Zestril has been found to be generally well tolerated in controlled clinical trials involving 2003 patients and subjects. The most frequent clinical adverse experiences in controlled trials were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range. For adverse experiences which occurred in more than 1% of patients and subjects treated with Zestril or Zestril plus hydrochlorothiazide in controlled clinical trials, comparative incidence data are listed in the table below.

Percent of Patients in Controlled Studies

	Zestril (n = 2003†) Incidence (discontinuation)	Zestril/Hydrochlorothiazide (n = 644) Incidence (discontinuation)	Placebo (n = 207) Incidence
Dizziness	6.3 (0.6)	9.0 (0.9)	1.9
Headache	5.3 (0.2)	4.3 (0.5)	1.9
Fatigue	3.3 (0.2)	3.9 (0.5)	1.0
Diarrhea	3.2 (0.3)	2.6 (0.3)	2.4
Upper Respiratory Symptoms	3.0 (0.0)	4.5 (0.0)	0.0
Cough	2.9 (0.4)	4.5 (0.8)	1.0
Nausea	2.3 (0.3)	2.5 (0.2)	2.4
Hypotension	1.8 (0.8)	1.6 (0.5)	0.5
Rash	1.5 (0.4)	1.6 (0.2)	0.5
Orthostatic Effects	1.4 (0.0)	3.4 (0.2)	1.0
Asthenia	1.3 (0.4)	2.0 (0.2)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.0)	0.5
Dyspnea	1.1 (0.0)	0.5 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.0
Paresthesia	0.8 (0.0)	2.0 (0.2)	0.0
Impotence	0.7 (0.2)	1.6 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.8 (0.6)	0.5
Back Pain	0.5 (0.0)	1.1 (0.0)	1.4
Nasal Congestion	0.3 (0.0)	1.2 (0.0)	0.0
Decreased Libido	0.2 (0.1)	1.2 (0.0)	0.0
Vertigo	0.1 (0.0)	1.1 (0.2)	0.0

†Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in the controlled trials and rarer, serious, possibly drug related events reported in uncontrolled studies or marketing experience included: BODY AS A WHOLE: Chest discomfort, fever, flushing. CARDIOVASCULAR: Angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, palpitation. DIGESTIVE: Abdominal pain, anorexia, constipation, flatulence. METABOLISM: Gout. MUSCULOSKELETAL: Joint pain, shoulder pain. NERVOUS SYSTEM/PSYCHIATRIC: Depression, somnolence, insomnia, stroke. RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain. UROGENITAL: Oliguria, progressive azotemia, acute renal failure. OTHER: Blurred vision, pruritus, urinary tract infection, vasculitis of the legs. ANGIOEDEMA: Angioedema has been reported in patients receiving Zestril (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with Zestril should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.) HYPOTENSION: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. (See WARNINGS.) In patients with congestive heart failure, hypotension occurred in 5.0% and syncope occurred in 1.0% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients. **Clinical Laboratory Test Findings. Serum Electrolytes:** Hyperkalemia (See PRECAUTIONS.) **Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with Zestril alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased. **Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with Zestril but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. **Other (Causal Relationship Unknown):** Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%), and serum potassium (0.4%). **OVERDOSAGE.** The oral LD_{50} of lisinopril is greater than 20 g/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. **DOSAGE AND ADMINISTRATION. Initial Therapy:** In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20-40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with Zestril alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of Zestril. **Diuretic Treated Patients:** In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of Zestril. The diuretic should be discontinued, if possible, for two or three days before beginning therapy with Zestril to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of Zestril should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with Zestril alone, diuretic therapy may be resumed as described above. If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) Concomitant administration of Zestril with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.) **Use in Elderly:** In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of Zestril. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution. **Dosage Adjustment in Renal Impairment:** The usual dose of Zestril (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance > 10 mL/min ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine-Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	>30	10
Moderate to Severe Impairment	≥10 ≤30	5
Dialysis Patients	<10	2.5‡

‡Dosage or dosing interval should be adjusted depending on the blood pressure response. Rev E 12/87

Distributed by: **Stuart Pharmaceuticals,** Division of ICI Americas Inc, Wilmington, DE 19897.

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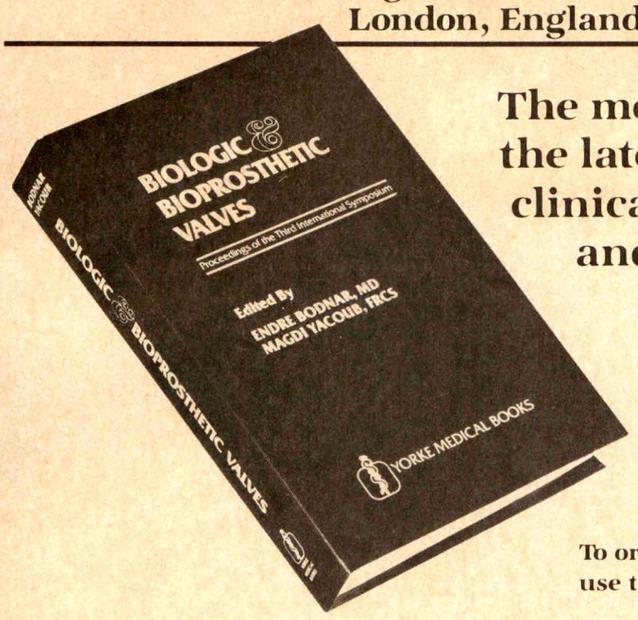
Biologic & Bioprosthetic Valves

Proceedings of the Third International Symposium
London, England, May 21-23, 1985



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The Third International Symposium on Cardiac Bioprostheses was held May 21-23, 1985, at the Grosvenor House Hotel, London. Six years have passed since the first meeting of this kind was held in Munich and 3 years since the second conference in Rome. The reassessment of the state of the art with biologic and bioprosthetic valves seems to have become a regular 3-yearly fixture reflecting the fast development of these devices, as well as the desire of surgeons and academics working in this field to share experiences, exchange ideas, and to resolve problems together.

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The Editors are eminently qualified to do this book, Dr. Bodnar is with the Cardiothoracic Institute, London, England, and Mr. Yacoub is with Harefield Hospital, Middlesex, England.

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691 Acute Effects of Felodipine in Exertional Angina Pectoris

Sabino Scardi, Claudio Pandullo, Fulvio Pivotti, Giuliano Ceschia, and Giorgio Pollavini

To investigate antianginal efficacy, duration of action and tolerability, 2 doses of the new calcium antagonist felodipine were studied in 15 patients with stable exertional angina pectoris. Five and 10 mg of felodipine and placebo were randomly given, in double-blind conditions, on 3 different days. Exercise tests were performed 3 and 10 hours after dosing. In comparison with placebo, the 2 felodipine doses significantly increased anginal and ischemic thresholds as well as duration of exercise and total work to peak exercise, at both 3 and 10 hours after administration. At the third hour, the 2 doses of the active drug were equally effective while after 10 hours felodipine 10 mg was superior to the lower dose in total work at the onset of angina as well as in total work and duration of exercise at peak exercise. A single administration of felodipine, 5 and 10 mg, may improve exercise capacity over a 10-hour period in patients with stable exercise angina due to atherosclerotic heart disease.

697 Correlation of Minimum Coronary Lumen Diameter with Left Ventricular Functional Impairment Induced by Atrial Pacing

Jonathan Tobis, David Sato, Orhan Nalcioglu, Warren D. Johnston, John Mallery, Jackie See, Lian Qu, Tim Reese, Jim Paynter, Steve Montelli, and Walter L. Henry

To understand whether quantitative measurement of minimal coronary luminal diameter is a better method than percent diameter narrowing for assessing the functional impairment of myocardial contractility produced by coronary artery stenoses, measurements were made from 37 stenotic segments in 27 patients with coronary artery disease and from corresponding segments in 10 subjects without coronary artery narrowing. An assessment of the reliability of the 2 types of measurements was made by correlating them with the physiologic parameters of both segmental wall motion and global ejection fraction response induced by atrial pacing. A minimal lumen diameter of ≤1.5 mm identified patients who were likely to have a functional impairment during atrial pacing as assessed by either global ejection fraction or segmental wall motion defects. The results demonstrate that the measurement of minimal lumen diameter is more accurate than measurements of percent narrowing in predicting the effects of an atrial pacing stress test on segmental wall motion. We conclude that minimal coronary luminal diameter provides a better method than percent diameter narrowing calculations to measure the anatomic severity of coronary artery narrowing.

704 Recruitment and Baseline Description of Patients in the Cardiac Arrhythmia Pilot Study

The Cardiac Arrhythmia Pilot Study (CAPS) Investigators

The Cardiac Arrhythmia Pilot Study tested the feasibility of performing a large-scale study to evaluate the effect of therapy of ventricular arrhythmias after acute myocardial infarction (AMI). Patients with ≥10 ventricular premature complexes/hour, recorded 6 to 60 days after AMI, and with an ejection fraction >0.20 were randomized to receive encainide, flecainide, imipramine, morcizine or placebo. Successful therapy was defined as ≥70% suppression of ventricular premature complexes and >90%

Continued on page A28

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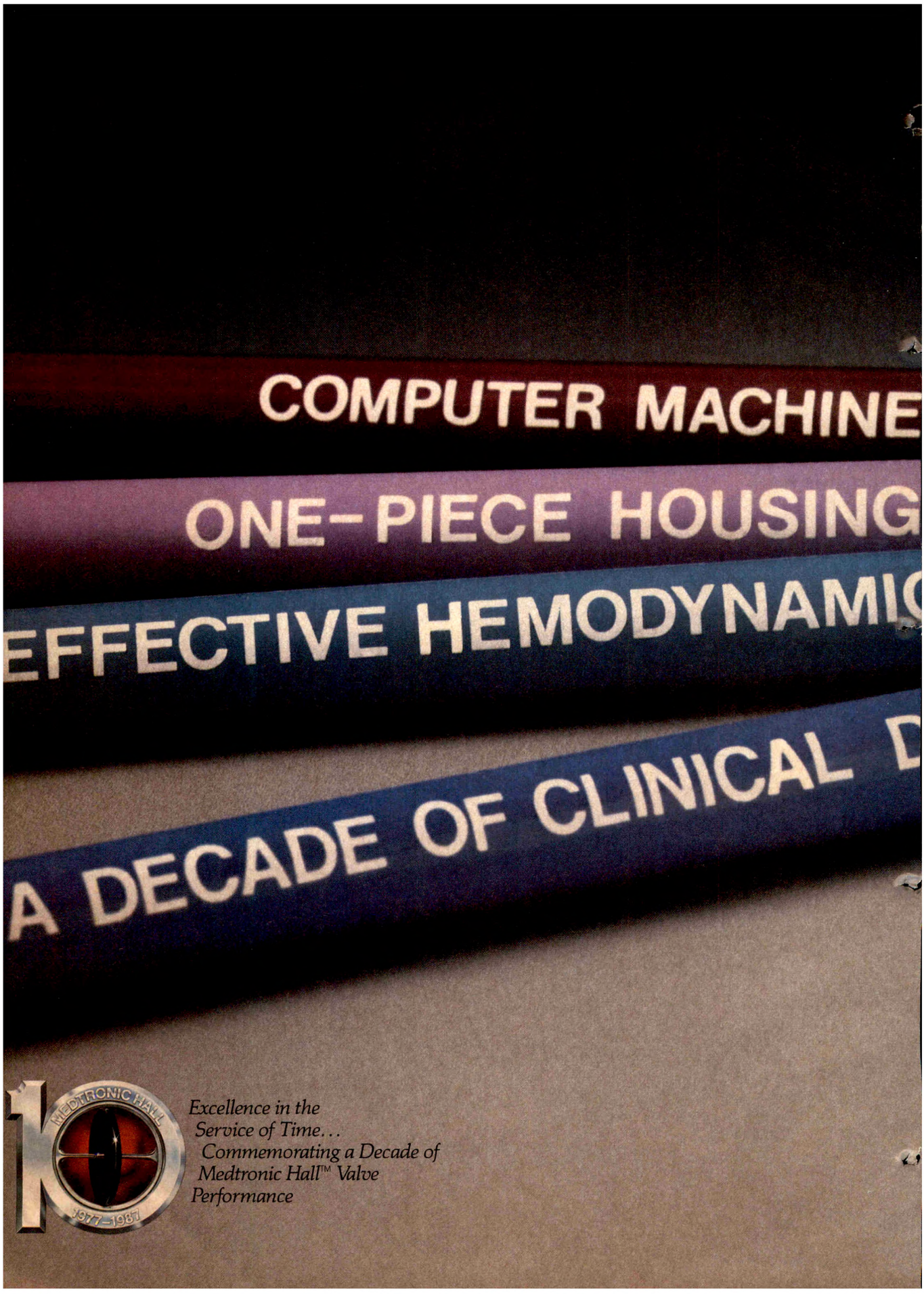
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suppression of runs of ventricular tachycardia. One-half of patients were randomized within 1 month after their AMI. The mean ejection fraction was 0.45. Approximately one-third of all patients had at least 1 run of unsustained ventricular tachycardia. Over 20 AMI- and age-eligible patients were identified to obtain each randomized patient. The randomization process successfully distributed baseline variables across drug groups.

714 Prevalence and Significance of Atrial Fibrillation in Coronary Artery Disease (CASS Registry)

Airlie Cameron, Miles J. Schwartz, Richard A. Kronmal, and Andrzej S. Kosinski

Atrial fibrillation (AF) was present in 116 (0.6%) of 18,343 patients with angiographically demonstrated coronary artery disease. The presence of AF was positively associated with the following clinical and angiography variables: older age, sex (male), mitral regurgitation and functional impairment due to congestive heart failure. The number of diseased coronary arteries was negatively related to the presence of AF. Atrial fibrillation was an independent predictor of survival and its presence doubled the estimated risk over those patients without AF.

718 Helicopter Transport of Patients During Acute Myocardial Infarction

Raye L. Bellinger, Robert M. Califf, Daniel B. Mark, Rita A. Weber, Patricia Collins, Janice Stone, Harry R. Phillips, III, Lawrence German, and Richard S. Stack

This study examines the initial experience of a regional helicopter system transporting patients with acute myocardial infarction, with particular attention to complications encountered. Over a 15-month period, 250 patients were transported. Most patients received thombolytic therapy before or during transport. The most frequent complication was transient hypotension (21 patients), usually treated with fluid boluses. Third-degree atrioventricular block and nonsustained ventricular tachycardia were the next most common. There were no instances of ventricular fibrillation, asystole or respiratory arrest in-flight. No patient required cardioversion, defibrillation or intubation during transport. Five patients received cardiopulmonary resuscitation in-flight; in 3, cardiopulmonary resuscitation had been started before liftoff. We conclude that complications are infrequent during emergency helicopter transport of patients with acute myocardial infarction. The cost/benefit ratio of such a transport system, however, remains to be determined.

723 Comparison of Two Dose Regimens of Intravenous Tissue Plasminogen Activator for Acute Myocardial Infarction

Eric J. Topol, Barry S. George, Dean J. Kereiakes, Richard J. Candela, Charles W. Abbottsmith, David C. Stump, Jane Boswick, Richard S. Stack, Robert M. Califf, and the TAMI Study Group

We compared 2 dosing schedules of intravenous tissue plasminogen activator (t-PA) for acute myocardial infarction in a multicenter trial. For the first 178 patients (group A), 60 mg was given in the first-hour dose and 90 mg was infused over 7 hours. In the subsequent 208 patients (group B), the first-hour dose was 1.0 mg/kg, with additional 150 mg given over 5 hours.

Continued on page A41

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A Brief Summary follows.

> The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

INDICATIONS AND USAGE: Oral procainamide is indicated in the treatment of premature ventricular contractions, ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS: Hypersensitivity to procainamide is an absolute contraindication. In this connection, cross-sensitivity to procaine and related drugs must be borne in mind.

Procainamide should not be administered to patients with complete atrioventricular heart block. It is also contraindicated in cases of second degree and third degree A-V nodal block unless an electrical pacemaker is operative.

It has been suggested that procainamide be contraindicated in patients with myasthenia gravis.

WARNINGS: Granulocytopenia may follow the use of procainamide, and deaths from sepsis have occurred. Leukocyte changes are most likely to occur during the first three months of therapy. During this time routine blood counts should be done at least every two weeks and thereafter at longer intervals throughout maintenance procainamide therapy. Complaints of malaise and aches (a flu-type syndrome) are often reported in association with the granulocyte depression.

Patients should be instructed to report such symptoms promptly, as well as any soreness of mouth, throat or gums, unexplained fever, or symptoms of an upper respiratory tract infection. If these should occur and a complete blood count indicates a granulocyte depression, procainamide therapy should be discontinued immediately and appropriate treatment instituted. Recovery of leukocyte count usually occurs within a few weeks.

The incidence of granulocytopenia appears to be higher with procainamide sustained-release tablets than with standard tablets.

PRECAUTIONS: General— During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgment of mural thrombi and produce an embolic episode. However, it has been suggested that, in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient reevaluated since asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney disease, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Serious hypotension can result from peripheral vasodilation and from decreases in cardiac output. At high plasma levels, procainamide may produce sinus tachycardia due to reflex sympathetic response to its hypotensive effect. Large doses may increase cardiac automaticity and can induce complete atrioventricular block, cardiac standstill, or ventricular extrasystoles that may proceed to ventricular fibrillation. These effects on the myocardium are reflected in the electrocardiogram: a widening of the QRS complex occurs most consistently; less regularly, the P-R and Q-T intervals are prolonged; and the QRS and T waves show some decrease in voltage.

Antinuclear antibodies (ANA) are often found in patients receiving long-term procainamide therapy. The induction of ANA appears to be independent of dosage. Patients with procainamide-induced increases in ANA titers may develop a syndrome resembling systemic lupus erythematosus (SLE). The mechanism of this syndrome is uncertain. Polyarthralgia, arthritic symptoms, and pleuritic pain are common symptoms; to a lesser extent fever, myalgia, skin lesions, pleural effusion, pericarditis, headache, fatigue, weakness, nausea and abdominal pain may occur. Rare cases of thrombocytopenia, Coombs' positive hemolytic anemia, increased SGOT, SGPT, and serum amylase have been reported which may be related to this SLE-like syndrome.

It is recommended that tests for systemic lupus erythematosus be carried out at regular intervals in patients receiving maintenance or prolonged procainamide therapy. The drug should be discontinued if there is a rising ANA titer or clinical symptoms of SLE appear. The SLE-like syndrome may be reversible upon discontinuation of the drug. If discontinuation does not cause remission of the symptoms, corticosteroid therapy may be effective. If the SLE-like syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, corticosteroid suppressive therapy may be used concomitantly with procainamide.

Information for Patient— Practitioners should give the following information and instructions to patients receiving Procan SR. 1. Do not crush or chew these tablets. Swallow them whole. 2. Take this medicine exactly as directed by your doctor. Do not miss any doses and do not take more medicine than ordered. Do not stop taking this medicine without first checking with your doctor. 3. If you miss a dose and remember within one hour or so, take it as soon as possible. Then go back to your regular dosing schedule. Do not take double doses. If you have any questions about this, check with your doctor. 4. Report to your doctor any flu-type symptoms, such as malaise and aches, as well as any soreness of the mouth, throat or gums, unexplained fever, skin rash, unusual bleeding or bruising, symptoms that resemble arthritis, or symptoms of an upper respiratory tract infection. 5. Do not be concerned if you occasionally notice in your stool something that looks like a tablet. In Procan SR (procainamide hydrochloride tablets), the drug is "held" in a wax core that has been specially designed to slowly release the drug for your body to absorb. When this process is completed the empty, nonabsorbable wax core, which looks nearly unchanged, is eliminated from your body. 6. Keep container tightly closed and store in a cool, dry place.

Procan® SR (procainamide hydrochloride tablets)

Laboratory Tests— Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals.

Routine blood counts are advisable during maintenance procainamide therapy. See WARNINGS for additional information.

Plasma concentrations of procainamide and NAPA should be monitored in patients with renal disease, hepatic disease, cardiac failure, or low cardiac output states.

Drug Interactions: 1. **Antiarrhythmics:** Concurrent use with procainamide may result in additive cardiac effects and/or additive toxic effects. 2. **Anticholinergics:** Procainamide enhances the anticholinergic effects. Extreme caution must be exercised with such a combination. 3. **Anticholinesterases:** Procainamide antagonizes the effect of anticholinesterases in myasthenia gravis, and paralysis returns. 4. **Antihypertensives:** Procainamide may potentiate the hypotensive effects of thiazide diuretics and other antihypertensive agents. Adjustment of dosage may be required. 5. **Histamine H_2-receptor antagonists:** It has been reported that histamine H_2-receptor antagonists such as cimetidine and ranitidine reduce renal clearance of procainamide and NAPA, resulting in higher plasma concentrations for longer durations. Caution should be exercised when administering these drugs concurrently, especially in the elderly, who have a reduced ability to clear all three. Dosage modification may be required. 6. **Neuromuscular Blocking Agents:** Procainamide potentiates the effects of skeletal muscle relaxants such as succinylcholine. It also may enhance or prolong the neuromuscular blocking activity of bacitracin, colistimethate, dihydrostreptomycin, gentamicin, gramicidin, kanamycin, neomycin, polymyxin B, streptomycin, and viomycin, producing respiratory depression.

Pregnancy— Pregnancy Category C. Animal reproduction studies have not been conducted with procainamide. It is also not known whether procainamide can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Procainamide should be given to a pregnant woman only if clearly needed.

Nursing Mothers— Procainamide and its major metabolite, NAPA, have been identified in breast milk. Caution should be exercised when procainamide is administered to a nursing woman.

ADVERSE REACTIONS: Most frequent, especially with large oral doses: 1. Anorexia; 2. Nausea; 3. Vomiting; 4. Diarrhea; 5. Urticaria; 6. Pruritus.

Less frequent: 1. Reactions in patients on long-term procainamide therapy: a. Antinuclear antibodies (ANA); b. Syndrome resembling systemic lupus erythematosus (SLE) (See PRECAUTIONS); 2. Hypersensitivity reactions: a. Angioneurotic edema; b. Maculopapular rash; c. Fever; d. Eosinophilia; e. Hypergammaglobulinemia.

Infrequent: 1. Granulocytopenia, sometimes resulting in death (See WARNINGS); 2. Convulsions; 3. Psychosis with hallucinations; 4. Confusion; 5. Mental depression; 6. Giddiness; 7. Lightheadedness; 8. Weakness; 9. Bitter taste.

Rare: 1. Hypotension; 2. A case was reported with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following a single dose of the drug.

OVERDOSAGE: Signs and Symptoms: Severe hypotension, ventricular fibrillation, widening of QRS complex, junctional tachycardia, intraventricular conduction delay, oliguria, lethargy, confusion, nausea, and vomiting.

Treatment: If ingestion is recent, emesis, activated charcoal, or gastric lavage may reduce absorption. Dopamine, phenylephrine, or levarterenol may be helpful in reversing severe hypotensive responses.

Management of overdosage includes symptomatic treatment with ECG and blood pressure monitoring. Procainamide toxicity can usually be treated, if necessary, by administering vasopressors after adequate fluid volume replacement. Intravenous infusion of 1/6 molar sodium lactate injection reportedly reduces the cardiotoxic effects of procainamide.

If procainamide toxicity causes severe hypotension and renal insufficiency, urinary elimination of procainamide and NAPA is decreased, and hemodialysis may be required. Hemodialysis significantly reduces the serum half-life of procainamide, and effectively removes procainamide and NAPA. Peritoneal dialysis is not effective.

It has been reported that one patient who ingested approximately 7 grams of procainamide hydrochloride recovered after treatment consisting of IV levarterenol, IV furosemide, attempted volume expansion with albumin, and hemodialysis. Also reported is the case of an elderly patient who recovered after ingestion of approximately 19 grams of procainamide hydrochloride. The patient was treated with IV isoproterenol and IV epinephrine. The latter report suggested that insertion of a ventricular pacing electrode is a reasonable precautionary measure in case high grade A-V block develops.

Storage Conditions: Protect from moisture. Store bottles below 30°C (86°F). Store unit-dose packages at controlled room temperature, 15°-30°C (59°-86°F).

Caution— Federal law prohibits dispensing without prescription. 0207G014

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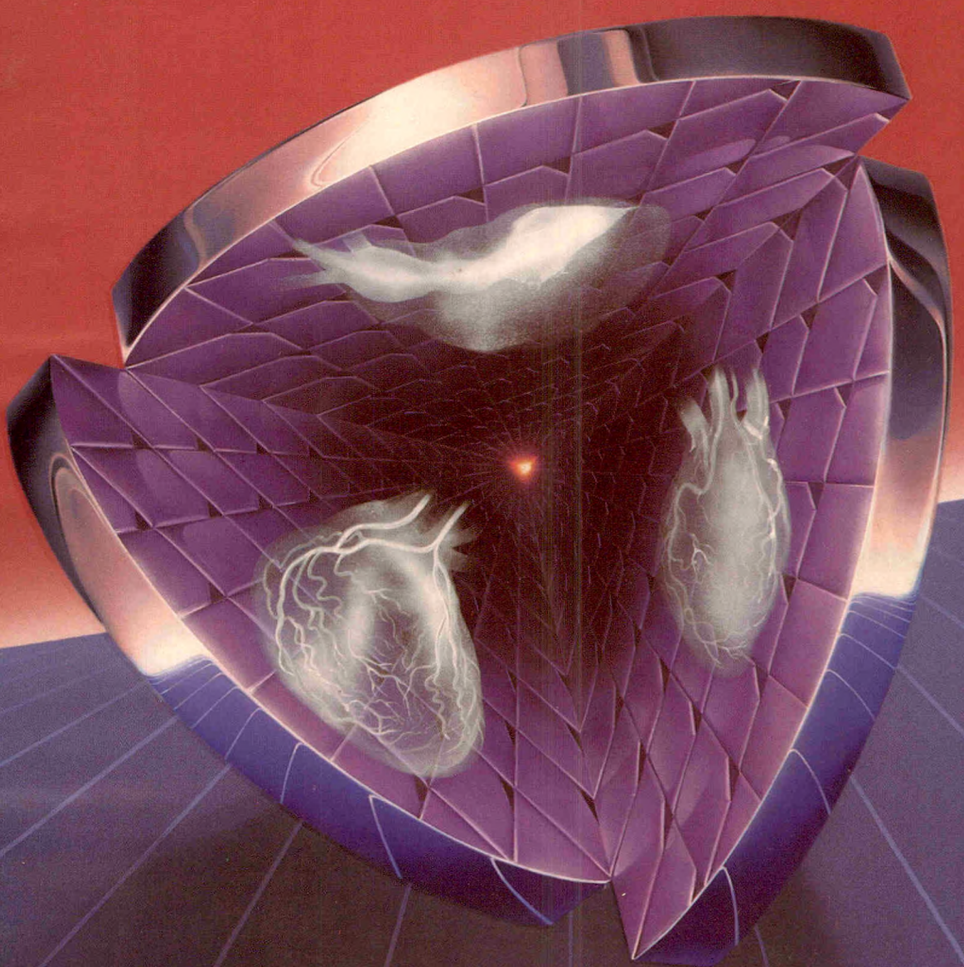
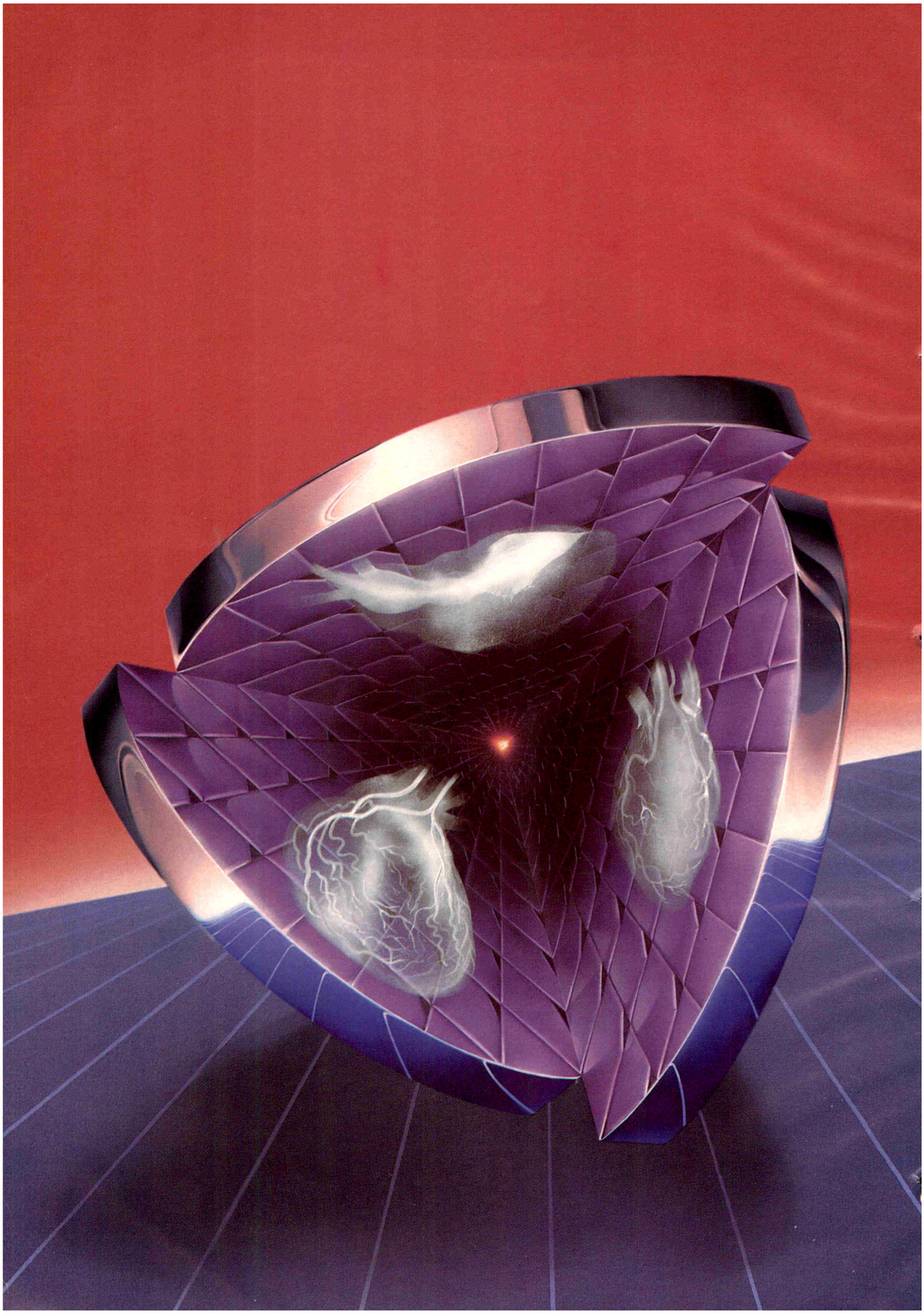
The image of safety.





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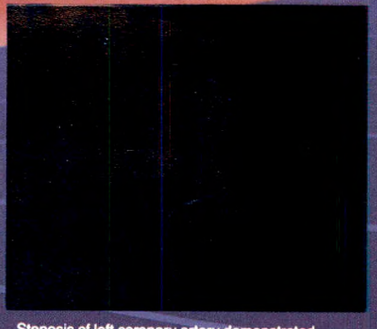

Stenosis of left coronary artery demonstrated with OMNIPAQUE.

NONIONIC

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(IOHEXOL)

An ongoing record of safety in angiocardiography.

See next page for important product information concerning contraindications, warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations.

OMNIPAQUE® 240 300 350

INJECTION (IOHEXOL) INTRAVASCULAR

PLEASE CONSULT FULL PRODUCT INFORMATION BEFORE USING.
A SUMMARY FOLLOWS:

DESCRIPTION: OMNIPAQUE is a nonionic, water-soluble radiographic contrast medium for intravascular administration in concentrations of 240, 300, and 350 mgI/mL. Each milliliter of iohexol solution contains 1.21 mg tromethamine and 0.1 mg edetate calcium disodium with the pH adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide, but it contains no preservatives.

CONTRAINDICATIONS: OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

WARNINGS: OMNIPAQUE should be used with extreme care in patients with severely impaired renal and/or hepatic function; severe thyrotoxicosis, hyperthyroidism, or an autonomously functioning thyroid nodule; diabetes with a serum creatinine level above 3 mg/dL. It is not recommended for use in patients with anuria.

Patients with known or suspected pheochromocytoma should receive a minimum of contrast medium if the benefit of the examination is judged to outweigh its risk; blood pressure should be monitored throughout the procedure, and measures for the treatment of hypertensive crisis should be readily available.

Contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly those with therapeutically resistant anuria. The combination of contrast agent and dehydration may precipitate myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over age 40, should be considered before instituting intravascular administration of contrast agents.

Ionic contrast media, when injected intravenously or intra-arterially, may promote sickling in individuals who are homozygous for sickle cell disease.

PRECAUTIONS: Diagnostic procedures that involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself. Competent personnel and emergency facilities should be available, since severe delayed reactions have been reported (see ADVERSE REACTIONS). The possibility of serious, life-threatening, fatal, anaphylactoid, or cardiovascular reactions should always be considered (see ADVERSE REACTIONS). It is of utmost importance that a course of action be carefully planned in advance for immediate treatment of serious reactions. Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, in diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease). *Patients should be well hydrated prior to and following iohexol administration.* Careful consideration of the potential risk of acute renal failure should be given before performing excretory urography in diabetic patients with diabetic nephropathy and in susceptible nondiabetic patients (often elderly with preexisting renal disease). Immediately following surgery, excretory urography should be used with caution in renal transplant recipients. The possibility of an idiosyncratic reaction in susceptible patients should always be considered (see ADVERSE REACTIONS). The susceptible population includes, but is not limited to, patients with a history of a previous reaction to contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity: bronchial asthma, hay fever, and food allergies. A thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast media, may be more accurate than pretesting in predicting potential adverse reactions.

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS). Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered and administered using separate syringes. Recent reports indicate that such pretreatment does not prevent serious, life-threatening reactions but may reduce both their incidence and severity.

Even though the osmolality of OMNIPAQUE is low compared to diatrizoate- or iothalamate-based ionic agents of comparable iodine concentration, the potential transitory increase in circulatory osmotic load in patients with congestive heart failure requires caution during injection. These patients should be observed for several hours following the procedure to detect delayed hemodynamic disturbances.

General anesthesia may be indicated in the performance of some procedures in selected adult patients; however, a higher incidence of adverse reactions has been reported in these patients and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of the anesthesia which can reduce cardiac output and increase the duration of exposure to the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria, because of the risk of inducing thrombosis and embolism.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be borne in mind during the catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

Selective coronary arteriography should be performed only in those patients in whom the expected benefits outweigh the potential risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

When OMNIPAQUE is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

The inhibitory effects of nonionic contrast media on mechanisms of hemostasis have been shown, in vitro, to be less than those of ionic contrast media at comparable concentrations. For this reason, standard angiographic procedures should always be followed: angiographic catheters should be flushed frequently, and prolonged contact of blood with contrast media in syringes and catheters should be avoided.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Parenteral products should be inspected and discarded if particulate matter or discoloration is present.

Drug/Laboratory Test Interaction: If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast medium administration. Thyroid function tests which do not depend on iodine estimation, eg, T_3 resin uptake or direct thyroxine assays, are not affected. Many radiopaque contrast agents are incompatible in vitro with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenesis, or whether OMNIPAQUE can affect fertility in men or women.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits with up to 100 times the recommended human dose. No evidence of impaired fertility or harm to the fetus has been demonstrated due to OMNIPAQUE. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known to what extent iohexol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Usually mild to moderate in severity. However, serious, life-threatening, and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media, including OMNIPAQUE. The injection of contrast media is frequently associated with the sensation of warmth and pain, especially in peripheral angiography; pain and warmth are less frequent and less severe with OMNIPAQUE than with many contrast media.

Cardiovascular System: Arrhythmias including PVCs and PACs (2%), angina/chest pain (1%), and hypotension (0.8%). Others including cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction were reported with an individual incidence of less than 0.4%. In controlled clinical trials involving 1,213 patients, one fatality occurred. A cause-and-effect relationship between this death and iohexol has not been established.

Nervous System: Vertigo [including dizziness and lightheadedness] (0.7%), pain (3%), photomas (2%), headache (2%), and taste perversion (1%). Others including anxiety, blurred vision, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis, and nystagmus were reported, with an individual incidence of less than 0.3%.

Respiratory System: Dyspnea and laryngitis, with an individual incidence of 0.1%.

Gastrointestinal System: Nausea (2%) and vomiting (0.6%). Others including diarrhea, dyspepsia, and dry mouth were reported, with an individual incidence of less than 0.2%.

Skin and Appendages: Urticaria (0.3%) and purpura (0.1%).

General Adverse Reactions to Contrast Media: The following reactions have been reported after administration of other intravascular iodinated contrast media, and rarely with iohexol. *Reactions due to technique:* hematomas and ecchymoses. *Hemodynamic reactions:* vein cramp and thrombophlebitis following intravenous injection. *Cardiovascular reactions:* rare cases of cardiac arrhythmias, reflex tachycardia, chest pain, cyanosis, hypertension, hypotension, peripheral vasodilatation, shock, and cardiac arrest. *Renal reactions:* occasionally, transient proteinuria; rarely, oliguria or anuria. *Allergic reactions:* asthmatic attacks, nasal and conjunctival symptoms, dermal reactions such as urticaria with or without pruritus, as well as pleomorphic rashes, sneezing, and lacrimation; rarely, anaphylactic reactions. Rare fatalities have occurred due to these or unknown causes. *Signs and symptoms related to the respiratory system:* pulmonary or laryngeal edema, bronchospasm, dyspnea; or *to the nervous system:* restlessness, tremors, convulsions. *Other reactions:* flushing, pain, warmth, metallic taste, nausea, vomiting, anxiety, headache, confusion, pallor, weakness, sweating, localized areas of edema (especially facial cramps), neutropenia, and dizziness. Rarely, immediate or delayed rigors can occur, sometimes accompanied by hyperpyrexia. Infrequently, "iodism" (salivary gland swelling) from organic iodinated compounds appears 2 days after exposure and subsides by the sixth day.

In general, the reactions that are known to occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Approximately 95% of adverse reactions accompanying the use of water-soluble intravascularly administered contrast agents are mild to moderate in degree. However, severe, life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred. Reported incidences of death range from 6.6 per 1 million (0.00066%) to 1 in 10,000 (0.01%). Most deaths occur during injection or 5 to 10 minutes later, the main feature being cardiac arrest, with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005%) patients.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast media, the dose, and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of dose injected, the speed of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that in the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Most adverse reactions to injectable contrast media appear within 1 to 3 minutes after the start of injection, but delayed reactions may occur.

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with angiocardiography than with other procedures. Cardiac decompensation, serious arrhythmias, angina pectoris, or myocardial ischemia or infarction may occur during angiocardiography and left ventriculography. Electrocardiographic and hemodynamic abnormalities occur less frequently with OMNIPAQUE than with diatrizoate meglumine and diatrizoate sodium injection.

OVERDOSAGE: Overdosage may occur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms include cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma, and cardiac arrest. Treatment of an overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

The intravenous LD_{50} values of OMNIPAQUE (in grams of iodine per kilogram body weight) are 24.2 in mice and 15.0 in rats.

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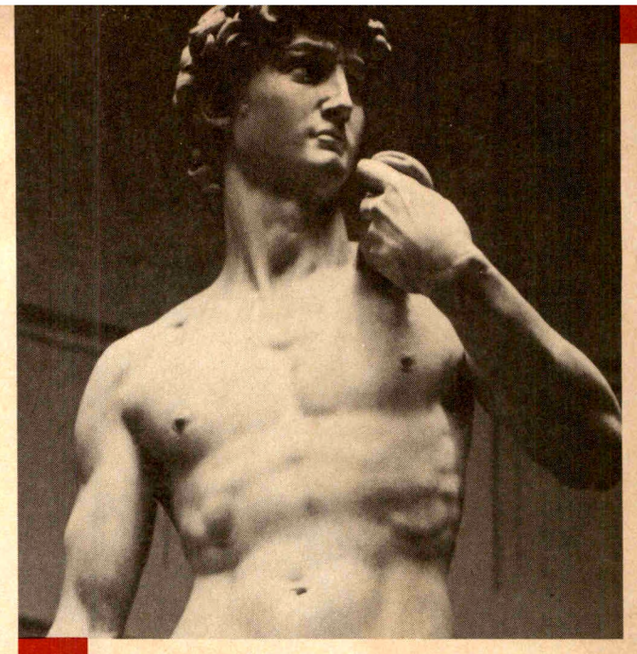

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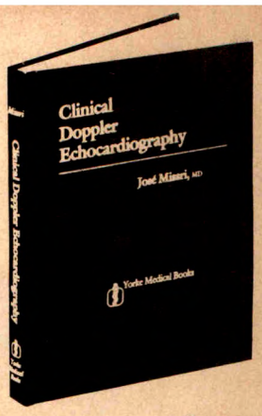

Clinical Doppler Echocardiography

by José Missri, MD
0-914316-51-6 256 pp., April 1986, 175 illustrations, $55.00

The development and refinement of Doppler echocardiography represent a major advance in the diagnostic applications of ultrasound in heart disease.

Dr. Missri has written *Clinical Doppler Echocardiography* to provide clinical cardiologists, postdoctoral fellows and "echo" technologists with practical information on cardiac Doppler applied to acquired and congenital disease.

Clearly written, logically presented, generously illustrated—including 4-color examples of Doppler color-flow mapping—and thoroughly indexed, *Clinical Doppler Echocardiography* is a must addition for personal and medical center libraries.

Table of Contents (in brief)

INTRODUCTION TO DOPPLER ECHOCARDIOGRAPHY
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EVALUATION OF CARDIAC FUNCTION AND ASSESSMENT OF CARDIOMYOPATHY BY DOPPLER ECHOCARDIOGRAPHY
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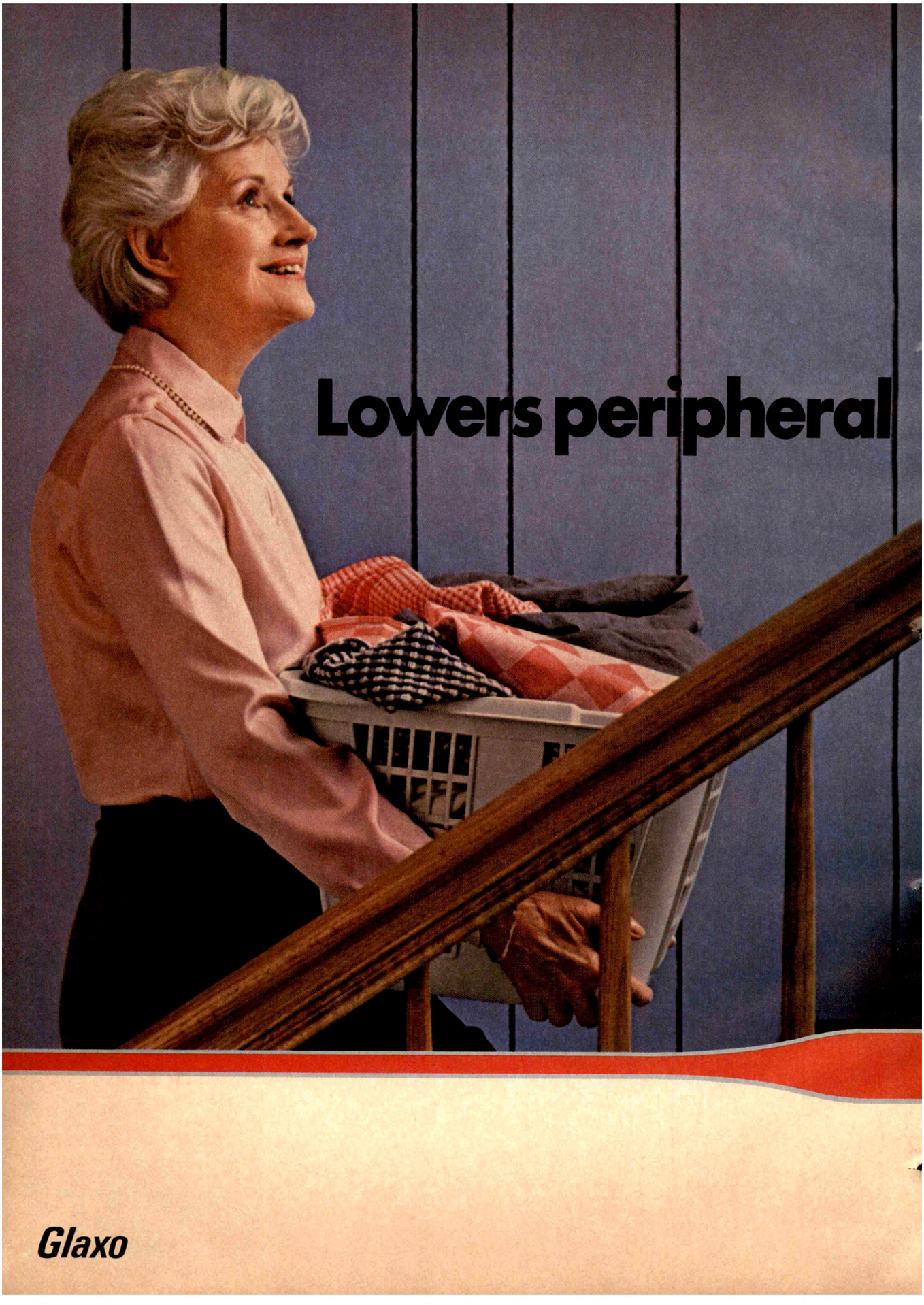
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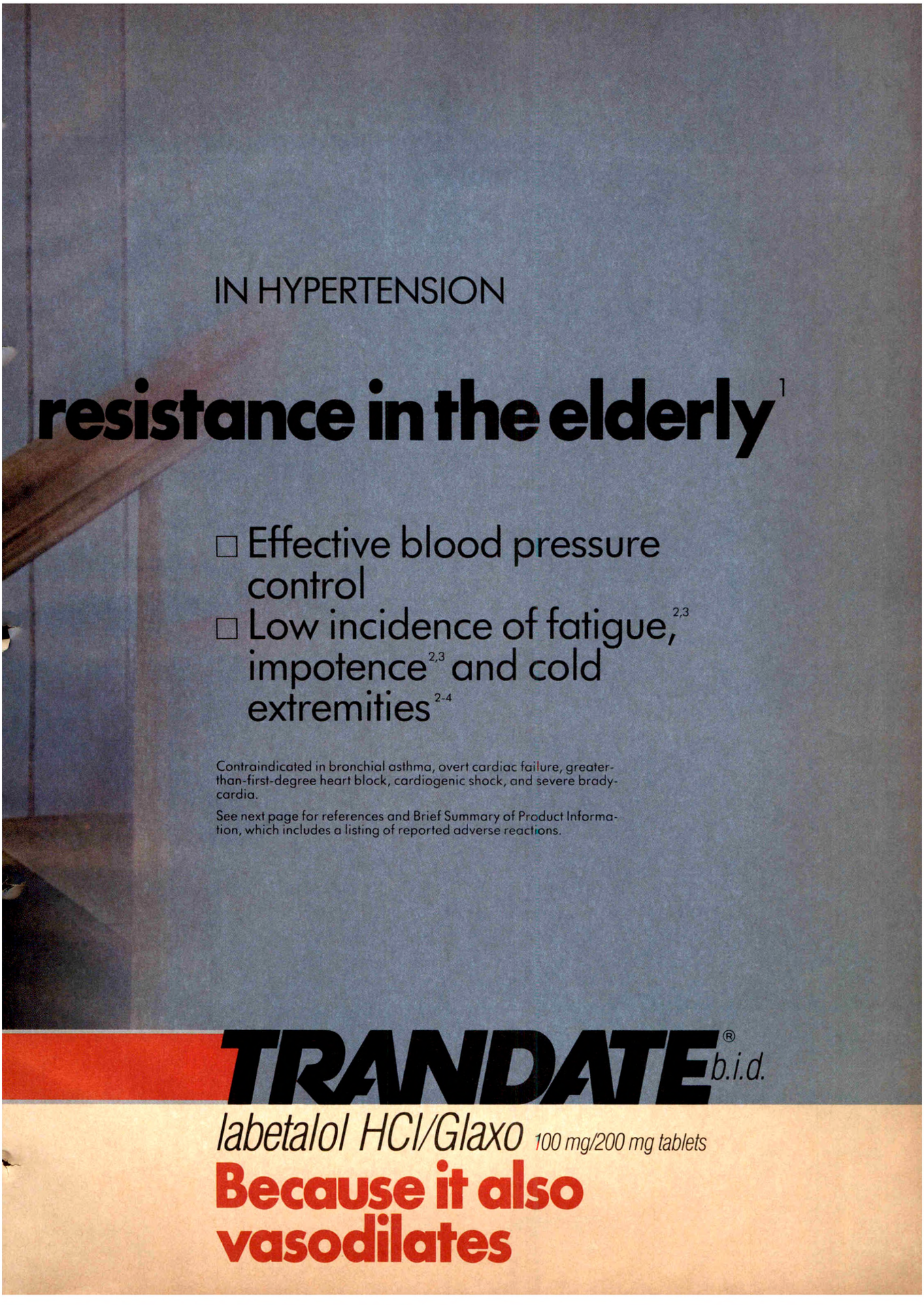
IN HYPERTENSION
resistance in the elderly[1]
☐ Effective blood pressure control
☐ Low incidence of fatigue,[2,3] impotence[2,3] and cold extremities[2-4]
Contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia.
See next page for references and Brief Summary of Product Information, which includes a listing of reported adverse reactions.
TRANDATE® b.i.d.
labetalol HCl/Glaxo 100 mg/200 mg tablets
Because it also vasodilates

References: 1. Holtzman JL, Finley D, Johnson B, et al: The effects of single-dose atenolol, labetalol, and propranolol on cardiac and vascular function. *Clin Pharmacol Ther* 1986;40:268-273. **2.** Due DL, Giguere GC, Plachetka JR: Postmarketing comparison of labetalol and propranolol in hypertensive patients. *Clin Ther* 1986;8(6):624-631. **3.** Burris JF, Goldstein J, Zager PG, et al: Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:1-9. **4.** Erb RJ, Plachetka JR: Thermographic evaluation of the peripheral vascular effects of labetalol and propranolol. *Curr Ther Res* 1985;28(1):68-73.

TRANDATE® Tablets
(labetalol hydrochloride)

BRIEF SUMMARY OF PRODUCT INFORMATION

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

INDICATIONS AND USAGE: TRANDATE® Tablets are indicated in the management of hypertension. TRANDATE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).

PRECAUTIONS: General: ***Impaired Hepatic Function:*** TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multi-center, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, and headache.

Gastrointestinal: Nausea (6%), vomiting, dyspepsia, diarrhea, and taste distortion.

Central and Peripheral Nervous Systems: Dizziness (11%), paresthesia, and drowsiness.

Autonomic Nervous System: Nasal stuffiness, ejaculation failure, impotence, and increased sweating.

Cardiovascular: Edema and postural hypotension.

Respiratory: Dyspnea.

Skin: Rash.

Special Senses: Vision abnormality and vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems: Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment.

Collagen Disorders: Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes: Dry eyes.

Immunological System: Antimitochondrial antibodies.

Liver and Biliary System: Cholestasis with or without jaundice.

Musculoskeletal System: Muscle cramps; toxic myopathy.

Respiratory System: Bronchospasm.

Skin and Appendages: Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia.

Urinary System: Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System: Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance or neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Allergic: Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic: Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal: Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

HOW SUPPLIED: TRANDATE® Tablets, 100 mg, light orange, round, scored, film-coated tablets engraved on one side with "TRANDATE 100 GLAXO," bottles of 100 (NDC 0173-0346-43) and 500 (NDC 0173-0346-44) and unit dose packs of 100 tablets (NDC 0173-0346-47).

TRANDATE Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with "TRANDATE 200 GLAXO," bottles of 100 (NDC 0173-0347-43) and 500 (NDC 0173-0347-44) and unit dose packs of 100 tablets (NDC 0173-0347-47).

TRANDATE Tablets, 300 mg, peach, round, scored, film-coated tablets engraved on one side with "TRANDATE 300 GLAXO," bottles of 100 (NDC 0173-0348-43) and 500 (NDC 0173-0348-44) and unit dose packs of 100 tablets (NDC 0173-0348-47).

TRANDATE Tablets should be stored between 2° and 30°C (36° and 86°F). TRANDATE Tablets in the unit dose boxes should be protected from excessive moisture.

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September 1986

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Research Triangle Park, NC 27709

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At initial angiography, 94 ± 30 minutes into therapy, the infarct vessel patency was 64% in group A versus 75% in group B ($p = 0.02$). However, bleeding was reduced in group B patients as evidenced by a decrease in requirement for ≥2 units of packed red blood cell transfusion (group A 36%, group B 27%, $p = 0.05$) and lower incidence of gastrointestinal bleeding (group A 12%, group B 4%, $p = 0.002$). To further study the importance of weight adjustment, patients were divided into 2 groups according to weight (≤90 kg vs >90 kg). According to the results, lighter weight patients had greater transfusion requirements (35% vs 20%, $p = 0.006$) and more frequent major bleeding episodes (16% vs 7%, $p = 0.025$). Thus, a higher, weight-adjusted first-hour dose of intravenous t-PA, with a shorter duration of maintenance infusion, is associated with: (1) improved infarct vessel patency; (2) more rapid recanalization; and (3) less bleeding complications without more fibrinogenolysis.

729 Evaluation of a QRS Scoring System for Estimating Myocardial Infarct Size. VI: Identification of Screening Criteria for Non-Acute Myocardial Infarcts

William D. Anderson, Nancy B, Wagner, Kerry L. Lee, Richard D. White, James Yuschak, Victor S. Behar, Ronald H. Selvester, Raymond E. Ideker, and Galen S. Wagner

Fifty-four criteria in a 32-point QRS scoring system for estimating myocardial infarct (MI) size from the standard 12-lead electrocardiogram were analyzed to identify those with high specificity and maximal sensitivity in detecting the presence of non-acute MI. Sensitivity was tested in a population consisting of 122 patients with single anterior or inferior MIs, while specificity was determined in a population of 500 normal subjects. Three MI screening criteria were selected using a stepwise logistic regression analysis: (1) aVF: Q wave ≥30 ms, (2) V_2: R ≤10 ms and ≤0.1 mV and (3) V_1: R ≥40 ms. The cumulative sensitivity was 80% while maintaining specificity at ≥95%.

734 Development and Validation of an Automated Method of the Selvester QRS Scoring System for Myocardial Infarct Size

James E. Pope, Nancy B. Wagner, David Dubow, John H. Edmonds, Galen S. Wagner, and W. Kenneth Haisty, Jr.

The Selvester QRS score for estimation of myocardial infarct size from the standard 12-lead electrocardiogram has not yet experienced general clinical acceptance primarily because it is limited by manual application of the 54 criteria. This study examined the electrocardiograms of 438 patients to develop software for an automated method of the Selvester system. After a comprehensive validation process involving extensive interactions between the manual scorer and the developer of the software, an automated method of Selvester scoring was generated that had a high correlation with manual application of the system ($r = 0.94$) and was superior regarding time, training, reproducibility of criteria selection and precision of waveform measurements.

739 Significance of Q-Wave Regression After Transmural Acute Myocardial Infarction

Santiago Coll, Amadeo Betriu, Tomás de Flores, Eulalia Roig, Ginés Sanz, Luis Mont, Jorge Magriñá, Antonio Serra, and Francisco Navarro-López

The prevalence and clinical implications of Q-wave loss after transmural acute myocardial infarction were assessed in a series of 313 consecutive patients. After a mean follow-up of 65 (1 to 100) months, 34 patients lost their Q waves. The time interval from the acute myocardial infarction to the first electrocardiogram showing Q-wave disappearance was 14 (1 to 32) months. The peak creatine kinase value was higher in patients who retained their Q waves than in those who lost them. The severity of coronary artery disease was similar in both groups, but patients with a normalized electrocardiogram had lower left ventricular end-diastolic pressure, higher ejection fraction and fewer abnormally contracting segments than their counterparts; in addition, no patient with Q-wave regression presented with left ventricular aneurysm. Although differences in mortality, nonfatal reinfarction and new onset of angina between the 2 groups were not significant, congestive heart failure was prevalent among patients with permanent Q waves. These findings suggest a smaller infarct size in patients showing Q-wave regression.

743 Limitations in the Interpretation of Rest-Exercise Ejection Fraction Changes After Early Thrombolytic Therapy During Acute Myocardial Infarction

Florence H. Sheehan, Detlef G. Mathey, Joachim Schofer, Suzanne Mitten, and Edward L. Bolson

The effect of exercise on left ventricular function was studied in 24 patients who underwent contrast ventriculography and supine bicycle exercise >2 weeks after acute myocardial infarction treated with intracoronary streptokinase. The ejection fraction response correlated poorly with the exercise response of motion in the infarct region ($r = 0.38$). In only half of patients whose infarct and noninfarct regions responded to exercise in opposing directions did the ejection fraction response reflect the response in the infarct region. The regional response to exercise better distinguished reperfused from nonreperfused patients than did the global response. Thus, the efficacy of thrombolytic therapy in salvaging myocardium is more accurately evaluated from the rest-exercise change in regional wall motion.

749 Use of Initial ST-Segment Deviation for Prediction of Final Electrocardiographic Size of Acute Myocardial Infarcts

Harry R. Aldrich, Nancy B. Wagner, Jane Boswick, Anne T. Corsa, Michael G. Jones, Peer Grande, Kerry L. Lee, and Galen S. Wagner

Because the decision to administer thrombolytic therapy for limitation of acute myocardial infarction (AMI) size must occur when only the history, physical examination and 12-lead electrocardiogram of a patient are

Continued on page A46

The benefit of antianginal protection plus safety...

CARDIZEM®: A FULLER LIFE

diltiazem HCl/Marion

60 mg 90/120 mg GREATER DOSAGE FLEXIBILITY

- ***A remarkable safety profile***[1-6]
  The low incidence of side effects with Cardizem allows patients to feel better.
- ***Protection against angina attacks***[1,5,7-9]
  The predictable efficacy of Cardizem in stable exertional and vasospastic angina allows patients to do more.*
- ***A decrease in myocardial oxygen demand***
  Resulting from a lowered heart rate-blood pressure product.[5]
- ***Compatible with other antianginals***[6]†
- ***Safe in angina with coexisting hypertension, COPD, asthma, or PVD***[1,3,5,6]

**CARDIZEM® (diltiazem HCl) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.*

†See Warnings and Precautions.

Please see brief summary of prescribing information on the next page.

0778A8

CARDIZEM® ANTIANGINAL PROTECTION PLUS SAFETY

diltiazem HCl/Marion

Usual maintenance dosage range: 180-360 mg/day

BRIEF SUMMARY
Professional Use Information

CARDIZEM®
(diltiazem HCl)
30 mg, 60 mg, 90 mg, and 120 mg Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), and (4) patients who have demonstrated hypersensitivity to the drug.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/ postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.
Nervous System:	Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.
Gastrointestinal:	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.
Dermatologic:	Petechiae, pruritus, photosensitivity, urticaria.
Other:	Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established. Issued 6/87

See complete Professional Use Information before prescribing.

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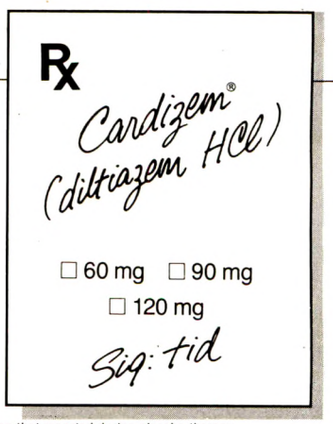

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available, a method that could quickly assess the amount of jeopardized myocardium would be of great clinical value. This retrospective study compared the epicardial injury (STΔ) on the admission electrocardiogram to the final AMI size estimated by the Selvester QRS score on the predischarge electrocardiogram to generate formulas able to predict the ultimate extent of AMI from the admission STΔ in 148 patients receiving no interventions aimed at reperfusion:

$$\text{Anterior AMI} = 3[1.5(\text{number leads } ST\uparrow) - 0.4];$$

$$\text{Inferior} = 3[0.6(AT\uparrow \text{ II, III, aVF}) + 2.0].$$

These formulas based on the extent of initial STΔ are predictive of the final AMI size and may be useful in determining the efficacy of acute reperfusion therapy.

754 Usefulness of Lactate Dehydrogenase and Lactate Dehydrogenase Isoenzymes for Diagnosis of Acute Myocardial Infarction

Gregg J. Reis, Harvey W. Kaufman, Gary L. Horowitz, and Richard C. Pasternak

The marginal benefit of lactate dehydrogenase (LD) and LD isoenzymes was reviewed in a retrospective analysis of 247 patients with cardiac enzymes ordered over a 1-month period. Of these, only 2 (0.8%) had acute myocardial infarction (AMI) with *normal* creatine kinase and creatine kinase MB but *abnormal* LD isoenzymes. Seven patients had false-positive LD isoenzymes. Thus, the routine use of LD and LD isoenzymes was of no use in the vast majority (96%) of patients and led to an incorrect diagnosis of AMI more often than it helped with the correct diagnosis. Total 1-month charges for LD and LD isoenzymes were $42,450. Therefore, it appears that LD and LD isoenzymes are not routinely useful in the diagnosis of AMI and it is suggested that they be ordered only under suspicion of late presentation (>48 hours) of AMI.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

759 Direct and Autonomically Mediated Effects of Oral Flecainide

Paolo Alboni, Nelly Paparella, Riccardo Cappato, and Gian Carlo Candini

The electrophysiologic modes of action of oral flecainide were assessed in 15 patients with normal sinus node and atrioventricular node. Two electrophysiologic studies were performed in each patient. In the first, the variables of the 2 nodes were evaluated both in the basal state and after autonomic blockade (propranolol 0.2 mg/kg and atropine 0.04 mg/kg). Oral flecainide was administered for 4 to 5 days (200 to 250 mg daily) and the study was then repeated with the same methods. In the basal state, flecainide did not change significantly the sinus node measures (overall effect); in contrast, after autonomic blockade, these measures were increased ($p < 0.01$) by the drug (direct depressant effect). Flecainide increased significantly the atrioventricular node measures both in the basal state and after autonomic blockade ($p < 0.01$), but the degree of increase was more marked after autonomic blockade ($p < 0.05$). These data provide evidence of dual effects of oral flecainide: a direct depressant action and an autonomically mediated opposing action, likely of a vagolytic type.

Continued on page A50

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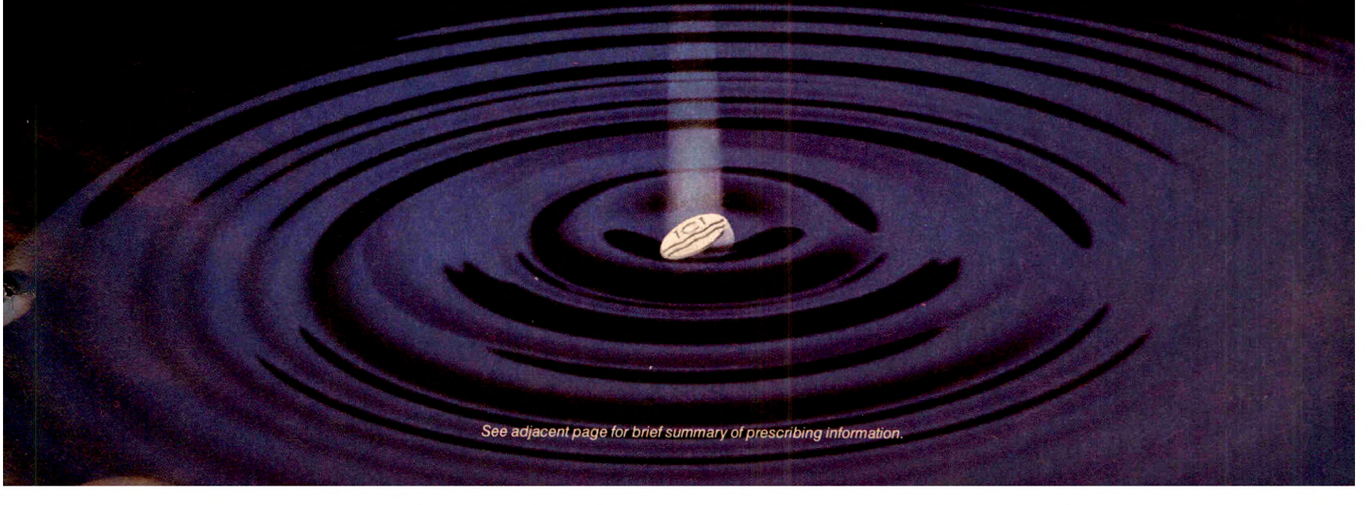

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DESCRIPTION: TENORMIN (atenolol), a synthetic, $beta_1$-selective (cardioselective) adrenoreceptor blocking agent, may be chemically described as benzeneacetamide, 4-[2′-hydroxy-3′-[(1 methylethyl) amino] propoxy]-. Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophilic compound with a water solubility of 26.5 mg/mL at 37°C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1N HCl (300 mg/mL at 25°C) and less soluble in chloroform (3 mg/mL at 25°C).

TENORMIN is available as 50 mg and 100 mg tablets for oral administration.

Inactive Ingredients: magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN should be withdrawn. (See Dosage and Administration.)

Cessation of Therapy With TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with other beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. To date, there has been no report of myocardial infarction or severe angina upon withdrawal of TENORMIN, probably due to its long plasma half-life. Because of the problems encountered with other beta blockers, when discontinuation of TENORMIN is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinstituted, at least temporarily. (See Dosage and Administration.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg, and a $beta_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: As with all beta-receptor blocking drugs it may be decided to withdraw TENORMIN before surgery. In this case, 48 hours should be allowed to elapse between the last dose and anesthesia. If treatment is continued, care should be taken when using anesthetic agents which depress the myocardium such as ether, cyclopropane, and trichloroethylene.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents (eg, dobutamine or isoproterenol with caution—see section on Overdosage). Manifestations of excessive vagal tone (eg, profound bradycardia, hypotension) may be corrected with atropine (1-2 mg IV).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See Dosage and Administration.)

PRECAUTIONS: Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (See Dosage and Administration.)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human dose, did not indicate a carcinogenic potential in rodents. Results of various mutagenicity studies support this finding.

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human dose), and increased incidence of atrial degeneration of hearts of male rats at 300 mg but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human dose, respectively).

USAGE IN PREGNANCY: Pregnancy Category C. Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human dose. Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. Frequency estimates were derived from controlled studies in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN (atenolol) and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects for TENORMIN and placebo is similar, causal relationship is uncertain.

The following adverse-reaction data present frequency estimates in terms of percentages: first from the US studies (volunteered side effects) and then from both US and foreign studies (volunteered and elicited side effects):

US STUDIES (% ATENOLOL-% PLACEBO):

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (0%-0.5%), postural hypotension (2%-1%), leg pain (0%-0.5%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (4%-1%), vertigo (2%-0.5%), lightheadedness (1%-0%), tiredness (0.6%-0.5%), fatigue (3%-1%), lethargy (1%-0%), drowsiness (0.6%-0%), depression (0.6%-0.5%), dreaming (0%-0%)

GASTROINTESTINAL: diarrhea (2%-0%), nausea (4%-1%)

RESPIRATORY (See WARNINGS): wheeziness (0%-0%), dyspnea (0.6%-1%)

TOTALS US AND FOREIGN STUDIES:

CARDIOVASCULAR: bradycardia (3%-0%), cold extremities (12%-5%), postural hypotension (4%-5%), leg pain (3%-1%)

CENTRAL NERVOUS SYSTEM/NEUROMUSCULAR: dizziness (13%-6%), vertigo (2%-0.2%), lightheadedness (3%-0.7%), tiredness (26%-13%), fatigue (6%-5%), lethargy (3%-0.7%), drowsiness (2%-0.5%), depression (12%-9%), dreaming (3%-1%)

GASTROINTESTINAL: diarrhea (3%-2%), nausea (3%-1%)

RESPIRATORY (see WARNINGS): wheeziness (3%-3%), dyspnea (6%-4%)

MISCELLANEOUS: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and, in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

HEMATOLOGIC: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

ALLERGIC: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

CENTRAL NERVOUS SYSTEM: Reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation of time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics.

GASTROINTESTINAL: Mesenteric arterial thrombosis, ischemic colitis.

OTHER: Reversible alopecia, Peyronie's disease, erythematous rash, Raynaud's phenomenon.

MISCELLANEOUS: The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN during investigational use and foreign marketing experience. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. The most common effects expected with overdosage of a beta-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm, and hypoglycemia.

In the case of overdosage, treatment with TENORMIN should be stopped and the patient carefully observed. TENORMIN can be removed from the general circulation by hemodialysis. In addition to gastric lavage, the following therapeutic measures are suggested if warranted:

BRADYCARDIA: Atropine or another anticholinergic drug.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CONGESTIVE HEART FAILURE: Conventional therapy.

HYPOTENSION (DEPENDING ON ASSOCIATED FACTORS): Epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis.

BRONCHOSPASM: Aminophylline, isoproterenol, or atropine.

HYPOGLYCEMIA: Intravenous glucose.

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within 1 to 2 weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within 1 week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four hour control with once-daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once-a-day oral doses of 200 mg.

Patients with Renal Impairment: Since TENORMIN is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73 m^2 (normal range is 100-150 mL/min/1.73 m^2); therefore, the following maximum dosages are recommended for patients with renal impairment:

Creatinine Clearance (mL/min/1.73 m^2)	Atenolol Elimination Half-life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	50 mg every other day

Patients on hemodialysis should be given 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually over a period of about 2 weeks. Patients should be carefully observed and advised to limit physical activity to a minimum.

HOW SUPPLIED: Tablets of 50 mg atenolol, NDC 0310-0105 (round, flat, uncoated white tablets identified with ICI debossed on one side and 105 debossed on the other side, bisected) are supplied in bottles of 100 tablets and unit-dose packages of 100 tablets.

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A/11/86

*Cardioselectivity denotes a relative preference for β_1-receptors, located chiefly in cardiac tissue. This preference is not absolute.

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764 Noninvasive Evaluation of Indecainide for Serious Ventricular Tachyarrhythmia

Philip J. Podrid, Stephan Hohnloser, and Bernard Lown

Indecainide was administered to 16 patients with a history of a sustained ventricular tachyarrhythmia. Therapy involved acute loading dose followed by a brief maintenance period with efficacy evaluated noninvasively using monitoring and exercise testing. With the acute drug test, 9 of 16 patients responded. Of the 12 patients who received maintenance therapy, 4 responded to the drug. There was no correlation between dose, blood level and response to drug. Neurologic side effects occurred in 5 patients and 5 patients had arrhythmia aggravation. Left ventricular function was reduced by the drug in each patient. Indecainide is an effective drug in some highly selected patients.

770 Coupling Intervals of Ventricular Extrastimuli Causing Resetting of Sustained Ventricular Tachycardia Secondary to Coronary Artery Disease: Relation to Susbsequent Termination

Mark E. Rosenthal, Nicholas J. Stamato, Jesus M. Almendral, Charles D. Gottlieb, and Mark E. Josephson

Single and double ventricular extrastimuli (VE) were delivered during 80 and 42 sustained, uniform ventricular tachycardias (VT), respectively. Single VE reset 41 VT and terminated 8, while double VE reset 33 VT and terminated 13. Seven of 8 VT terminated with single VE and 12 of 13 VT terminated with double VE were initially reset with longer coupling intervals than those causing termination. Coupling intervals of VE were corrected for tachycardia cycle length. The mean corrected coupling interval of single and double VE initially resulting in VT resetting was significantly longer than those causing termination. If the longest corrected coupling interval at which resetting was noted with single VE was ≥ 0.75, then 7 of 34 (21%) VT terminated compared with only 1 of 46 (2%) if resetting was not seen by this corrected coupling interval ($p < 0.01$). Similarly, for double VE, if the longest coupling interval at which resetting was observed was ≥ 0.75, 13 of 31 (42%) VT terminated versus 0 of 10 if VT resetting was not observed by this coupling interval ($p < 0.02$). These findings demonstrate that critical coupling intervals may exist during the introduction of increasingly premature single and double VE where if resetting has not been observed, termination is unlikely.

775 Validation of Double-Spike Electrograms as Markers of Conduction Delay or Block in Atrial Flutter

Francisco G. Cosio, Fernando Arribas, José María Barbero, Carlos Kallmeyer, and Antonio Goicolea

Fragmented electrograms have been found by endocardial mapping of atrial flutter, often inscribing a double spike. It has been suggested that these electrograms may represent local conduction delays, probably supporting the reentrant circuit. Attempting to understand the meaning of these electrograms, we studied the changes induced by flutter entrainment from the coronary sinus or the anterior right atrium. Entrainment from the coronary sinus increased spike separation, suggesting rate-dependent conduction slowing during orthodromic penetration of the area. Entrainment from the anterior right atrium decreased spike separation,

Continued on page A57

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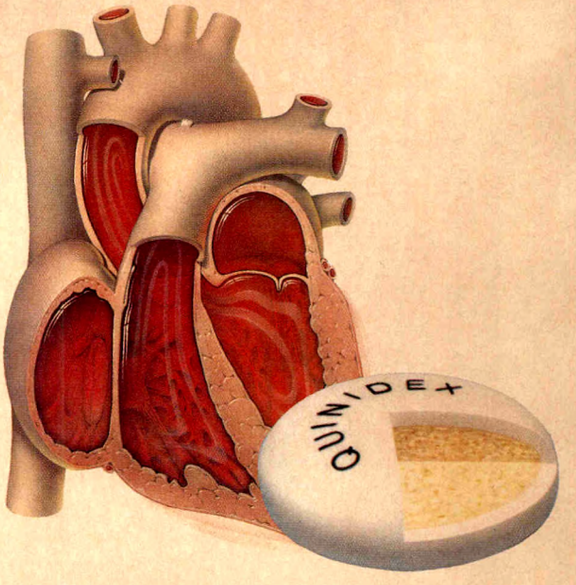

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Some patients may require t.i.d. dosing.

QUINIDEX EXTENTABS®

(Quinidine Sulfate, USP) 300mg

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Pharmaceutical Division, Richmond, Virginia 23261-6609

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Please see adjacent page for brief summary.

QUINIDEX
EXTENTABS®
(Quinidine Sulfate, USP)

The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4–8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	Effect
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Rev. June 1987

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LORELCO®
PROBUCOL 250 mg tablets

Prescribing Information appears on the last page.

Choose

LORELCO® PROBUCOL

250 mg tablets

as an adjunct to diet

Effectively Lowers Serum Cholesterol with a Unique Combination of Benefits

1 Efficacy

Lorelco works! You can prescribe it with confidence. Lorelco can virtually double the cholesterol-lowering efficacy of diet alone.[1] Total cholesterol-lowering efficacy *beyond diet* ranges from 10.7% to 27% in reported studies.[1-4]

2 Indications

Lorelco is specifically indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia who have not responded adequately to diet.

Consider the Whole Picture.

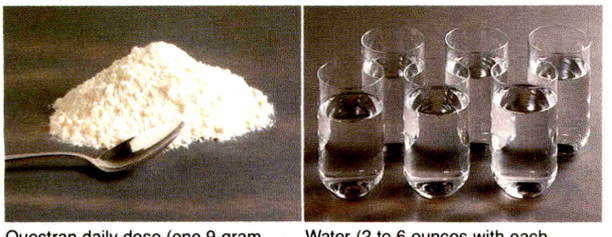
Merrell Dow

#1 selling lipid-lowering agent in the world

3 Compliance

The reasons for excellent compliance with Lorelco become clear with the taste and texture test.

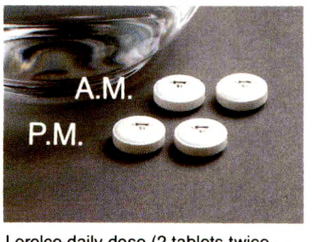
This



Questran daily dose (one 9-gram packet one to six times daily)

Water (2 to 6 ounces with each packet)

or This



Lorelco daily dose (2 tablets twice daily with meals)

Tablet counts in a 7 year study of Lorelco indicated that patients took over 90% of their scheduled dosage.[5]

4 Side Effects

Lorelco side effects are generally tolerable and of short duration.

Most frequent patient complaint is loose stools, which occur in about one in 10 patients and generally subside during therapy (see Prescribing Information for full discussion of side effects).

Lorelco is not an innocuous drug and strict attention should be paid to the Indications, Warnings, and Precautions.

5 Cost

The cost of Lorelco is significantly lower than that of the resins, lovastatin, and niacin tablets USV.

Cost can be a significant factor when therapy may have to be continued long-term, perhaps for years.

10 years of outstanding Lorelco performance[6]

Now prescribed in 27 countries

The effect of probucol-induced reduction of serum cholesterol or triglyceride levels or alteration of HDL-cholesterol levels on morbidity or mortality has not yet been established. Several years may be required before ongoing long-term investigations will resolve this question.

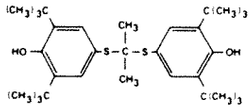
Prescribing Information appears on the last page.

References:
1. LeLorier J, et al: Diet and probucol in lowering cholesterol concentrations: additive effects on plasma cholesterol concentrations in patients with familial type II hyperlipoproteinemia. Arch Intern Med 1977; 137:1429-1434.
2. Mellies MJ, et al: Effects of probucol on plasma cholesterol, high and low density lipoprotein cholesterol, and apolipoproteins A1 and A2 in adults with primary familial hypercholesterolemia. Metabolism 1980; 29:956-964.
3. Polachek AA, et al: Probucol in the long-term treatment of hypercholesterolemia. Curr Med Res Opin 1973; 1:323-330.
4. Baker SG, et al: Treatment of homozygous familial hypercholesterolaemia with probucol. S Afr Med J 1982; 62:7-11.
5. McCaughan D: The long-term effects of probucol on serum lipid levels. Arch Intern Med 1981; 141:1428-1432.
6. Data on file, MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45242.

Lorelco® Tablets
(probucol tablets)

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION: Lorelco (probucol) film-coated tablets for oral administration contain 250 mg of probucol per tablet. Each tablet also contains as inactive ingredients: corn starch, ethylcellulose, glycerin, hydroxypropyl cellulose, hydroxypropyl methylcellulose 2910, iron oxide, lactose, magnesium stearate, microcrystalline cellulose, polysorbate 80, talc, and titanium dioxide. Lorelco is an agent for the reduction of elevated serum cholesterol. The chemical name is 4,4'-(isopropylidenedithio) bis (2,6-di-t-butylphenol). Its chemical structure does not resemble that of any other available cholesterol-lowering agent. It is lipophilic.



CLINICAL PHARMACOLOGY: Lorelco (probucol) lowers serum cholesterol and has relatively little effect on serum triglycerides. Patients responding to probucol exhibit a decrease in low density lipoprotein cholesterol. Cholesterol is reduced not only in the low density lipoprotein fraction, but also in some high density lipoprotein fractions with proportionately greater effect on the high density portion in some patients. Epidemiological studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease. The risk of lowering HDL-cholesterol while lowering LDL-cholesterol remains unknown. There is little or no effect reported on very low density lipoprotein.

Studies on the mode of action of Lorelco indicate that it increases the fractional rate of catabolism of low density lipoproteins. This effect may be linked to the observed increased excretion of fecal bile acids, a final metabolic pathway for the elimination of cholesterol from the body. Lorelco also exhibits inhibition of early stages of cholesterol synthesis and slight inhibition of absorption of dietary cholesterol. There is no increase in the cyclic precursors of cholesterol, namely desmosterol and 7-dehydrocholesterol. On this basis, it is concluded that Lorelco does not affect the later stages of cholesterol biosynthesis.

Absorption of Lorelco from the gastrointestinal tract is limited and variable. When it is administered with food, peak blood levels are higher and less variable. With continuous administration in a dosage of 500 mg b.i.d., the blood levels of an individual gradually increase over the first three to four months and thereafter remain fairly constant. In 116 patients treated with Lorelco for periods of three months to one year, the mean blood level was 23.6 ± 17.2 mcg/ml (± S.D.) ranging to 78.3 mcg/ml. Levels observed after seven years of treatment in 40 patients yielded an average value of 21.5 ± 16.5 mcg/ml (± S.D.) ranging to 62.0 mcg/ml.

At the end of 12 months of treatment in eight patients, blood levels averaged 19.0 mcg/ml. Six weeks after cessation of therapy, the average had fallen by 60 percent. After six months the average had fallen by 80 percent.

In December 1984 a National Institutes of Health Consensus Development Conference Panel1 concluded that lowering definitely elevated blood cholesterol levels (specifically blood levels of low-density lipoprotein cholesterol) will reduce the risk of heart attacks due to coronary heart disease. The effect of probucol-induced reduction of serum cholesterol or triglyceride levels or alteration of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not yet been established. Several years may be required before ongoing long-term investigations will resolve this question.

INDICATIONS AND USAGE: Serious animal toxicity has been encountered with probucol. See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections. Probucol is not an innocuous drug and strict attention should be paid to the INDICATIONS and WARNINGS.

Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Dietary therapy specific for the type of hyperlipidemia is the initial treatment of choice. Excess body weight may be an important factor and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory disease such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision ultimately is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

The selection of patients for cholesterol-lowering drug therapy should take into account other important coronary risk factors such as smoking, hypertension and diabetes mellitus. Consideration should be given to the efficacy, safety and compliance factors for each of the cholesterol-lowering drugs prior to selecting the one most appropriate for an individual patient.

Lorelco may be indicated for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoproteins) who have not responded adequately to diet, weight reduction and control of diabetes mellitus. Lorelco may be useful to lower elevated cholesterol that occurs in patients with combined hypercholesterolemia and hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.

It is not always possible to predict from the lipoprotein type or other factors which patients will exhibit favorable results. Lipid levels should be periodically assessed. Small or transient changes in high density lipoprotein cholesterol may be due to inaccuracies in the method of determination. Substantial changes are sometimes seen with diet.

The effect of probucol-induced reduction of serum cholesterol or triglyceride levels or alteration of HDL-cholesterol levels on morbidity or mortality due to coronary heart disease has not yet been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS: (See also PRECAUTIONS.) Lorelco is contraindicated in patients who are known to have a hypersensitivity to it.

WARNINGS: SERIOUS ANIMAL TOXICITY HAS BEEN ENCOUNTERED WITH PROBUCOL IN RHESUS MONKEYS FED AN ATHEROGENIC DIET AND IN BEAGLE DOGS. (SEE ANIMAL PHARMACOLOGY AND TOXICOLOGY SECTION.)

Although Q-T prolongation can occur in patients on probucol, the arrhythmias observed in monkeys fed large doses of probucol added to an atherogenic diet have not been reported in man; nevertheless, the following precautions are deemed prudent:

1. At the start of treatment with Lorelco and throughout the treatment period, patients should be advised to adhere to a low cholesterol, low fat diet.
2. As part of an overall evaluation, a baseline, six month, and one year repeat ECG tracing should be considered. If marked prolongation of the Q-T interval (after correction for rate) occurs, the possible benefits and risks should be carefully considered before making the decision to continue the probucol administration.

Lorelco should not be used in patients with evidence of recent or progressive myocardial damage or findings suggestive of ventricular arrhythmias.

No instances of increase in ectopy attributed to Lorelco have been reported. However, patients with unexplained syncope while on Lorelco should have ECG surveillance.

PRECAUTIONS

General: Because Lorelco is intended for long-term administration, adequate baseline studies should be performed to determine that the patient has elevated serum cholesterol levels. Serum lipid levels should be determined before treatment and repeated during the first few months of treatment and periodically thereafter. A favorable trend in cholesterol reduction should be evident during the first three to four months of administration of Lorelco. Probucol lowers serum total and LDL cholesterol, and also lowers HDL-cholesterol in many patients with elevated LDL-cholesterol. Epidemiologic studies within hypercholesterolemic populations have shown that serum HDL-cholesterol is an independent, inversely correlated, risk factor for coronary heart disease (see CLINICAL PHARMACOLOGY). Animal or human studies which could confirm or deny the hypothesis that drug induced alteration in HDL-cholesterol affects cardiovascular risk have not been carried out. It is not known whether probucol-induced reduction of serum HDL-cholesterol will affect cardiovascular risk since no long-term, controlled clinical trials of probucol for the prevention of coronary heart disease, similar to the LRC-CPPT (See CLINICAL STUDIES), have been performed. The probable benefits obtained from LDL-cholesterol reduction must be weighed against the possible risk of a reduction in HDL-cholesterol when assessing the response of each patient receiving Lorelco treatment. If satisfactory lipid alteration is not achieved, the drug should be discontinued.

Information for Patients: The patient should be instructed to adhere to a prudent diet. Females should be cautioned against becoming pregnant for at least six months after discontinuing Lorelco and should not breast feed their infants during therapy with Lorelco.

Laboratory Tests: The physician should schedule periodic blood lipid determinations and should consider periodic electrocardiograms. (See WARNINGS.)

Elevations of the serum transaminases (glutamic-oxalacetic and glutamic-pyruvic), bilirubin, alkaline phosphatase, creatine phosphokinase, uric acid, blood urea nitrogen and blood glucose above the normal range were observed on one or more occasions in various patients treated with Lorelco. Most often these were transient and/or could have been related to the patient's clinical state or other modes of therapy. Although the basis for the relationship between probucol and these abnormalities is not firm, the possibility that some of these are drug-related cannot be excluded. In the controlled trials, the incidence of abnormal laboratory values was no higher in the patients treated with probucol than in the patients who received placebo. If abnormal laboratory tests persist or worsen, if clinical signs consistent with the abnormal laboratory tests develop, or if systemic manifestations occur, probucol should be discontinued.

Drug Interactions: The addition of clofibrate to probucol is not recommended since the lowering effect on mean serum levels of either LDL or total cholesterol is generally not significantly additive and, in some patients, there may be a pronounced lowering of HDL-cholesterol. Neither oral hypoglycemic agents nor oral anticoagulants alter the effect of Lorelco on serum cholesterol. The dosage of these agents is not usually modified when given with Lorelco. Monkeys fed a high fat, high cholesterol diet admixed with probucol exhibited serious toxicity. The toxicity observed in monkeys has not been reported in man. (See WARNINGS and ANIMAL PHARMACOLOGY AND TOXICOLOGY sections.)

Carcinogenesis, Mutagenesis, Impairment of Fertility
In chronic studies of two years duration in rats, no toxicity or carcinogenicity was observed. These results are consistent with the lack of any adverse effect on fertility and the negative findings in tests for mutagenic activity in rats.

Pregnancy
Teratogenic Effects
Pregnancy—Category B: Reproduction studies have been performed in rats and rabbits at doses up to 50 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus due to probucol. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Furthermore, if a patient wishes to become pregnant, it is recommended that the drug be withdrawn and birth control procedures be used for at least six months because of persistence of the drug in the body for prolonged periods. (See CLINICAL PHARMACOLOGY.)

Labor and Delivery: The effect of Lorelco on human labor and delivery is unknown.

Nursing Mothers: It is not known whether this drug is secreted in human milk, but it is likely to be since such excretion has been shown in animals. It is recommended that nursing not be undertaken while a patient is on Lorelco.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Gastrointestinal
diarrhea or loose stools, flatulence, abdominal pain, nausea, vomiting, indigestion, gastrointestinal bleeding

Cardiovascular
prolongation of the Q-T interval on ECG

Neurologic
headache, dizziness, paresthesias, insomnia, tinnitus, peripheral neuritis

Hematologic
eosinophilia, low hemoglobin and/or hematocrit, thrombocytopenia

Dermatologic
rash, pruritus, ecchymosis, petechiae, hyperhidrosis, fetid sweat

Genitourinary
impotency, nocturia

Ophthalmic
conjunctivitis, tearing, blurred vision

Endocrine
enlargement of multinodular goiter

Idiosyncrasies
An idiosyncratic reaction observed with initiation of therapy and characterized by dizziness, palpitations, syncope, nausea, vomiting and chest pain has been observed.

Other
diminished sense of taste and smell, anorexia, angioneurotic edema

DRUG ABUSE AND DEPENDENCE: No evidence of abuse potential has been associated with Lorelco, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE: There is a single report of a 15 kg, three-year-old male child who ingested 5 gm of probucol. Emesis was induced by ipecac. The child remained well, apart from a brief episode of loose stools and flatulence. No specific information is available on the treatment of overdosage with Lorelco and no specific antidote is available. Probucol is not dialyzable. Treatment is symptomatic and supportive. Probucol has shown no identifiable acute toxicity in mice and rats. In these animals the LD_{50} (oral) is in excess of 5 gm/kg of body weight.

DOSAGE AND ADMINISTRATION: For adult use only. The recommended and maximal dose is 500 mg (two tablets of 250 mg each) twice daily with the morning and evening meals.

HOW SUPPLIED: Each white film-coated tablet contains 250 mg probucol and is imprinted with the DOW diamond trademark over the code number 51, or LORELCO 250.
Bottles of 120 tablets, a 30-day supply for one patient (NDC 0068-0051-52)

Keep well closed. Store in a dry place. Avoid excessive heat. Dispense in well closed light-resistant container with child-resistant closure.

ANIMAL PHARMACOLOGY AND TOXICOLOGY: In rhesus monkeys administration of probucol in diets containing unusually high amounts of cholesterol and saturated fat resulted in the death of four of eight animals after several weeks. Premonitory syncope was frequently observed and was associated with a pronounced prolongation of the Q-T intervals (30 to 50 percent longer than that observed in untreated monkeys). Serum levels of probucol greater than 20 mcg/ml were generally associated with some prolongation in the Q-T interval in the cholesterol-fed monkey. A 75 msec or greater increase in Q-T interval from control values was usually seen at 40 mcg/ml and above. Blood levels in humans receiving probucol average approximately 20 mcg/ml and not uncommonly reach levels of 40 mcg/ml and higher. Rhesus monkeys fed normal (low fat) chow and receiving probucol three to thirty times the human dose equivalent achieved blood levels only one-third those of many human subjects. No adverse effects were detected in these monkeys over an eight-year period of continuous drug administration. In another study in rhesus monkeys, an atherogenic diet was fed for two years and daily treatment with probucol, separated in time from the atherogenic meal, was carried out during the second year. Serum probucol levels ranged 20 to 50 mcg/ml in five of ten monkeys, and less in the remaining animals. Marked prolongation of the $Q\text{-}T_c$ interval in the electrocardiogram or syncopal behavior was never observed over the entire one-year treatment period. Regression of gross aortic lesions comparable to that observed in a parallel group of monkeys receiving cholestyramine was seen in animals receiving probucol. It should be emphasized that both HDL-cholesterol and LDL-cholesterol were markedly reduced in this regression study. During the performance of a two-year chronic study involving 32 probucol-treated dogs (beagles) there were 12 fatalities. Subsequent experiments have indicated that probucol sensitizes the canine myocardium to epinephrine, resulting in ventricular fibrillation in many dogs. Among the animal species in which probucol has been studied, the dog is peculiar with respect to the phenomenon of sudden death due to the sensitization of the myocardium to epinephrine. In contrast to findings in the dog, injections of epinephrine to probucol-treated monkeys did not induce ventricular fibrillation.

In other studies, monkeys were given probucol either before and after, or only after myocardial infarction induced by coronary artery ligation. In these studies there was no difference between probucol- and placebo-treated groups with respect to either survival or detailed blind quantitation of myocardial changes (gross and histopathologic).

Probucol has shown no identifiable toxicity in mice and rats. In these animals the LD_{50} (oral) is in excess of five gm/kg of body weight. In chronic studies of two-year duration in rats, no toxicity or carcinogenicity was observed.

From studies in rats, dogs and monkeys, it is known that probucol accumulates slowly in adipose tissue. Approximately 90 percent of probucol administered orally is unabsorbed. For that which is absorbed, the biliary tract is the major pathway for clearance from the body and very little is excreted by way of the kidneys.

Myocardial injury was produced in various groups of rats by one of the following procedures: aortic coarctation, coronary ligation, or cobalt or isoproterenol injection. After probucol administration, no deleterious effects related to treatment occurred as measured by survival and microscopic examination of myocardial damage.

Probucol was administered to minipigs beginning ten days before ligation of coronary artery and continued for 60 days post surgery. Challenge with epinephrine at the end of 60 days failed to induce ventricular fibrillation in any of the coronary-ligated, probucol-treated minipigs.

CLINICAL STUDIES: In a multicenter, randomized, double-blind study, the LRC-CPPT2, hypercholesterolemic patients treated with an oral bile acid sequestrant (cholestyramine) and a cholesterol lowering diet experienced average total and low-density lipoprotein cholesterol reductions greater than those obtained in the placebo group treated with diet alone. The cumulative seven-year incidence of the primary end point—combined incidence of definite CHD death and/or definite nonfatal myocardial infarction—was 7% in the cholestyramine group and 8.6% in the placebo group. This was a 19% reduction in risk (P less than 0.05, single-tail test) of the primary end point reflecting a 24% reduction in definite CHD death and a 19% reduction in nonfatal myocardial infarction.

The subjects included in the study were middle-aged men (35-59 years old) with serum cholesterol levels at least 265 mg/dl and no previous history of heart disease. It is not clear to what extent these findings can be extrapolated to other segments of the hypercholesterolemic population not studied.

The bile acid sequestrant, cholestyramine was used in the above trial. Caution should be exercised in extrapolating these results to probucol since it differs from cholestyramine with regard to its mode of action, spectrum of cholesterol-lowering potency, effect on HDL-cholesterol and possible toxicity. The effect of probucol-induced reduction of serum cholesterol levels on morbidity or mortality due to coronary heart disease has not yet been established. Several years may be required before ongoing long-term investigations will resolve this question.

REFERENCES:
1. Consensus Development Panel, Lowering blood cholesterol to prevent heart disease, *JAMA* 253: 2080-2086, 1985.
2. The Lipid Research Clinics Program: The Lipid Research Clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 251: 351-64, 1984.

Product Information as of April, 1986 Y196D

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suggesting fusion by antidromic penetration in the area. The findings are compatible with double spikes being a marker of local conduction delays included in the flutter circuit.

781 Characteristics of Entrainment During Autodecremental Atrial and Ventricular Stimulation

Agustin Castellanos, Liaqat Zaman, Pedro Fernandez, Bolivar Portillo, Barouh V. Berkovits, and Robert J. Myerburg

The entrainment of circus movement tachycardias during autodecremental pacing was analyzed in 9 patients with manifest Wolff-Parkinson-White syndrome. During autodecremental atrial stimulation, the phenomenon was observed in 34 of 38 episodes. Because this always occurred during Wenckebach sequences, the His bundle and ventricular cycle lengths were longer than the pacing cycle lengths. Thus, the definition of "classic" entrainment was not fulfilled. On the other hand, during autodecremental ventricular stimulation the phenomenon was seen in 79 of 80 episodes, invariably with the characteristics of the so-called "concealed" entrainment. In addition, because 115 of 118 (98%) of episodes were terminated, autodecremental pacing proved to be very effective in the treatment of circus movement tachycardia.

787 Sensitivity for Ventricular Tachyarrhythmias of an Automatic External Defibrillator in Patients Undergoing Electrophysiologic Studies

Mark D. Carlson, Charles S. Freeman, Hasan Garan, and Jeremy N. Ruskin

An automatic advisory external defibrillator (AED) was activated during all arrhythmias occurring at the time of 77 electrophysiologic studies in 45 patients. The device recommended "shock" during 36 of 55 (65%) episodes of sustained ventricular tachycardia (VT) and all 5 episodes of ventricular fibrillation. Of 10 episodes of nonsustained VT, 6 terminated after analysis was complete. The AED correctly advised "shock" for all 6 episodes. Thus, the sensitivity of the device for all ventricular arrhythmias was 47 of 66 (71%). The AED recommended "shock" for all 31 episodes of rapid VT and 1 of 2 episodes of atrial fibrillation associated with hypotension (32 of 33, 97%). The 19 episodes of VT for which "no shock" was advised were comparatively slow and hemodynamically well tolerated. The device recommended "no shock" during all 21 episodes of normal sinus rhythm and all 20 episodes of rapid atrial pacing analyzed. Thus, the specificity of the AED for wide complex tachyarrhythmias was 100%.

791 Determinants of Survival in Patients with Malignant Ventricular Arrhythmia Associated with Coronary Artery Disease

Steven Lampert, Bernard Lown, Thomas B. Graboys, Philip J. Podrid, and Charles M. Blatt

Patients with coronary artery disease and a history of malignant ventricular arrhythmia (defined as noninfarction ventricular fibrillation or hemodynamically compromising ventricular tachycardia) were followed for up to 9 years and the survival data were analyzed. In this group of 161 patients there were 57 deaths of which 35 (63%) were sudden. Life-table analysis demonstrated a 10% sudden death rate for all patients in the first year and a 7% annual rate in the subsequent 4 years. The likelihood of dying suddenly was related to the state of left ventricular function and the

Continued on page A63

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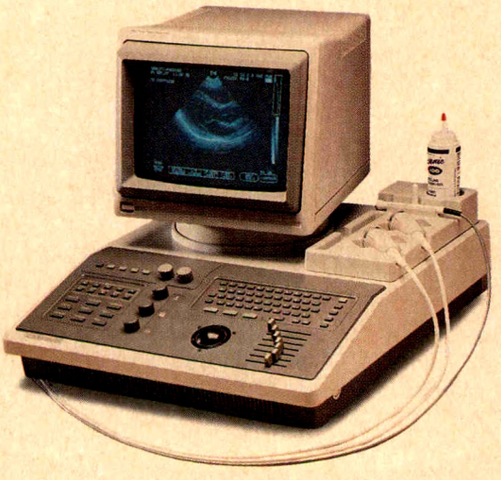

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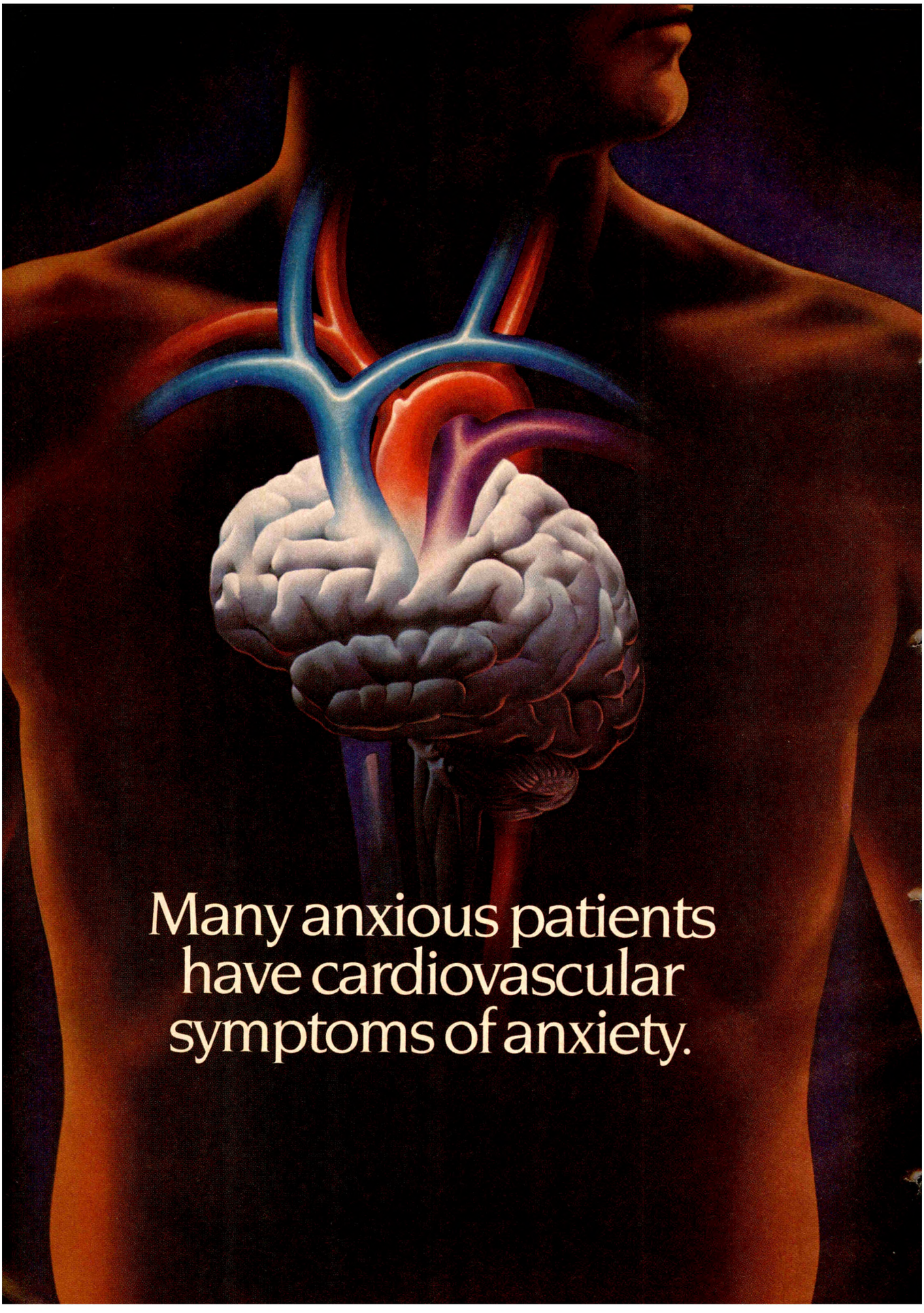
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have cardiovascular
symptoms of anxiety.

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In double-blind, four-week clinical trials in 976 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.[1]

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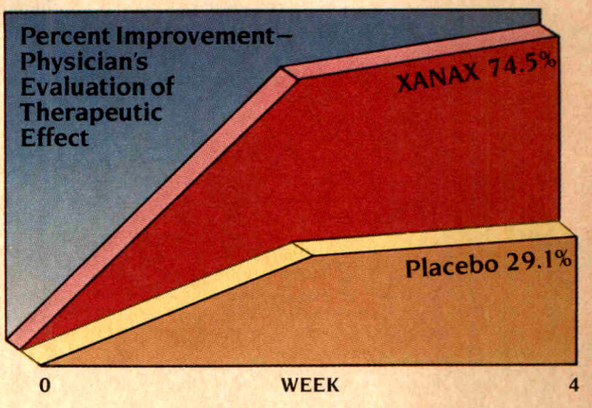

...including anxiety with associated cardiovascular symptoms...

Most patients in the study had cardiovascular symptoms even though cardiovascular disease was ruled out. XANAX was shown to effectively relieve anxiety with associated cardiovascular symptoms.

...and anxiety with associated depressive symptoms.

Over 70% of these patients experienced moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<0.014$) than placebo in improving depressed mood.

1. Cohn JB: Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. *J Clin Psychiatry* 1981;42:347-351.

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Please see adjacent page for brief summary of prescribing information.

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INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions:* No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal:* Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular:* Tachycardia/palpitations, and hypotension. *Sensory:* Blurred vision. *Musculoskeletal:* Rigidity and tremor. *Cutaneous:* Dermatitis/allergy. *Other side effects:* Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-7-S

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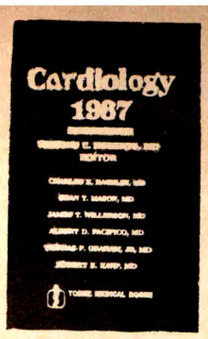

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presence of ventricular tachycardia during exercise tolerance testing on the discharge antiarrhythmic drug program. When the left ventricular ejection fraction was >30%, controlling ventricular arrhythmia improved survival, but when the ejection fraction was <30%, arrhythmia control did not affect survival. Multivariate regression analysis identified rales and exercise-induced ventricular tachycardia during antiarrhythmic drug therapy as the strongest predictors of sudden death.

SYSTEMIC HYPERTENSION

798 Effect of Behavior State on Caffeine's Ability to Alter Blood Pressure

Gwendolyn A. Pincomb, William R. Lovallo, Richard B. Passey, and Michael F. Wilson

Caffeine is known to produce acute blood pressure elevations in man. Hemodynamic mechanisms underlying its pressor effects and their possible health consequences have been disputed for years. Most previous studies involving measurements of cardiac output and vascular resistance have not used a placebo condition or controlled for behavioral interactions. In the current study caffeine's pressor effect was produced by either of 2 opposite mechanisms: enhanced vascular resistance at rest and potentiated cardiac stimulation during behavioral challenge. Implications for hemodynamic models, health consequences and for methodologic improvements in behavioral or clinical studies are discussed.

803 Lisinopril Versus Lisinopril plus Hydrochlorothiazide in Essential Hypertension

Jawahar Mehta, Larry M. Lopez, and Alfred D. Thorman

A new converting enzyme inhibitor, lisinopril, was administered alone or in combination with hydrochlorothiazide to patients with essential hypertension as initial pharmacotherapy. Both regimens lowered blood pressure significantly without causing tachycardia. The antihypertensive dose of lisinopril was lower when combined with hydrochlorothiazide. Metabolic alterations caused by hydrochlorothiazide, such as a decrease in serum potassium, were blunted by concurrent use of lisinopril. Side effects from both regimens were acceptable.

807 Comparison of the Antihypertensive Effects of Betaxolol to Atenolol

William J. Mroczek, James F. Burris, Leo B. Hogan, Daniel C. Citron, Allan H. Barker, and Robert H. McDonald

A randomized double-blind multicenter study compared a new oral β_1-adrenergic antagonist, betaxolol (10 to 40 mg) with atenolol (25 to 100 mg) once daily for 24 weeks in 146 patients with mild to moderate hypertension. During the initial titration phase, betaxolol produced a significantly greater reduction in supine diastolic blood pressure than atenolol when measured 24 hours after dosing. Through the remainder of the study, no significant differences in blood pressure reduction were noted between treatment groups. Of those patients completing the trial, a significantly greater number (72% for betaxolol vs 52% for atenolol) achieved a supine disastolic blood pressure of ≤90 mm Hg. Both drugs were well tolerated.

812 Comparative Study of Primary Tissue Failure Between Porcine (Hancock and Carpentier-Edwards) and Bovine Pericardial (Ionescu-Shiley) Bioprostheses in the Aortic Valve Position at Five- to Nine-Year Follow-Up

Ignacio Gallo, Francisco Nistal, Emilio Arbe, and Edurne Artiñano

We studied the incidence of primary tissue valve failure after 5 to 9 years of follow-up in 461 valves: 184 Hancock, 131 Carpentier-Edwards (C-E) and 146 Ionescu-Shiley (I-S). Cumulative follow-up was 1,016 patient-years for patients with Hancock valve, 688 for the C-E and 767 for the I-S group. Of the 397 prostheses at risk (154 Hancock, 120 C-E and 123 I-S), 36 instances of primary tissue valve failure occurred (12 Hancock, 7 C-E and 17 I-S). On an actuarial basis, the calculated probability of freedom from primary tissue valve failure was 88 ± 4% for the Hancock group, 87 ± 6% for the C-E and 51 ± 17% for the I-S at 9 years of follow-up. This represents a linearized incidence of 1.2 for the Hancock, 1 for the C-E and 2.2 failing valves per 100 patient-years for the I-S group. In a cohort of patients older than 40 years at the time of surgery, the rate of freedom from primary failure was 98 ± 1%, 87 ± 9% and 44 ± 22% for the Hancock, C-E and I-S groups, respectively, at 9 years. Comparison of actuarial curves disclosed a meaningful difference between the pericardial valve and the Hancock and C-E porcine bioprostheses at 9 years of follow-up.

817 Noninvasive Assessment of Mitral Stenosis Before and After Percutaneous Balloon Mitral Valvuloplasty

Patricia C. Come, Marilyn F. Riley, Daniel J. Diver, James P. Morgan, Robert D. Safian, and Raymond G. McKay

Balloon dilatation of the mitral valve was performed in 37 patients with symptomatic mitral stenosis. The procedure resulted in significant increases in valve areas measured by catheterization (0.9 ± 0.3 to 1.8 ± 0.8 cm^2) and by the Doppler pressure half-time technique (0.9 ± 0.2 to 1.7 ± 0.5 cm^2). In contrast to our previously reported correlation between Doppler and catheterization mitral valve areas ($r = 0.84$, $p < 0.001$), the area correlations before valvuloplasty in this selected group of patients with severe, symptomatic mitral stenosis was only fair ($r = 0.51$, $p < 0.002$). In addition, the correlation after valvuloplasty was again only fair ($r = 0.47$, $p < 0.005$). The increases in mitral valve area were independent of valve thickness assessed by 2-dimensional echocardiography. Flail mitral leaflet movement was not observed and the degree of mitral regurgitation, assessed by pulsed Doppler mapping techniques, increased by >1 of 4 grades in only 1 patient. A greater increase in lateral than in anteroposterior mitral orifice diameter suggested commissural splitting as the mechanism of successful valvuloplasty. Significant increases (all $p < 0.0001$) were noted in mitral valve EF slope, mitral valve excursion and cardiac output. Significant decreases (all $p < 0.001$) were observed in left atrial diameter and in mean catheterization and Doppler gradients.

Continued on page A71

TONOCARD®
(TOCAINIDE HCl|MSD)

INDICATIONS AND USAGE

TONOCARD is indicated for the treatment of life-threatening ventricular arrhythmias.

TONOCARD is also indicated for the treatment of some patients with symptomatic ventricular arrhythmias.

Because TONOCARD has the potential to produce serious hematologic disorders (0.18 percent in clinical trials) particularly leukopenia or agranulocytosis (sometimes fatal), the use of TONOCARD should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks. (See WARNINGS.) For less serious arrhythmias alternative therapy with less severe toxicity, such as certain beta-blocking agents, should be considered.

Like all other antiarrhythmics, tocainide has not been shown to prevent sudden death in patients with serious ventricular ectopic activity, and also, like all other antiarrhythmics, it has potentially serious adverse effects, including the ability to worsen arrhythmias. It is therefore essential that each patient given tocainide be evaluated electrocardiographically and clinically prior to, and during, tocainide therapy to determine whether the response to tocainide supports continued treatment.

CONTRAINDICATIONS

Patients who are hypersensitive to this product or to local anesthetics of the amide type.

Patients with second- or third-degree atrioventricular block in the absence of an artificial ventricular pacemaker.

WARNINGS

Blood Dyscrasias: Agranulocytosis, bone marrow depression, leukopenia, neutropenia, hypoplastic anemia, thrombocytopenia and sequelae such as septicemia and septic shock have been reported in patients receiving TONOCARD. Most of these patients received TONOCARD within the recommended dosage range. Fatalities have occurred (with approximately 25 percent mortality in reported agranulocytosis cases). Since most of these events have been noted during the first 12 weeks of therapy, it is recommended that complete blood counts, including white cell, differential and platelet counts be performed, optimally, at weekly intervals for the first three months of therapy, and periodically thereafter. Complete blood counts should be performed promptly if the patient develops any signs of infection (such as fever, chills, sore throat, or stomatitis), bruising, or bleeding. If any of these hematologic disorders is identified, TONOCARD should be discontinued and appropriate treatment should be instituted if necessary. Blood counts usually return to normal within one month of discontinuation. Caution should be used in patients with pre-existing marrow failure or cytopenia of any type. (See ADVERSE REACTIONS.)

Acceleration of Ventricular Rate: Acceleration of ventricular rate occurs infrequently when antiarrhythmics are administered to patients with atrial flutter or fibrillation (see ADVERSE REACTIONS).

PRECAUTIONS

General

Pulmonary Fibrosis: Pulmonary fibrosis, interstitial pneumonitis, fibrosing alveolitis, pulmonary edema, and pneumonia, possibly drug related, have been reported in patients receiving TONOCARD. Many of these events occurred in patients who were seriously ill. The experiences are usually characterized by bilateral infiltrates on x-ray and are frequently associated with dyspnea and cough. Fever may or may not be present. Patients should be instructed to promptly report the development of any pulmonary symptoms such as exertional dyspnea, cough, or wheezing. Chest x-rays are advisable at that time. If these pulmonary disorders develop, TONOCARD should be discontinued. (See ADVERSE REACTIONS.)

In patients with known heart failure or minimal cardiac reserve, TONOCARD should be used with caution because of the potential for aggravating the degree of heart failure.

Caution should be used in the institution or continuation of antiarrhythmic therapy in the presence of signs of increasing depression of cardiac conductivity.

In patients with severe liver or kidney disease, the rate of drug elimination may be significantly decreased (see DOSAGE AND ADMINISTRATION).

Since antiarrhythmic drugs may be ineffective in patients with hypokalemia, the possibility of a potassium deficit should be explored and, if present, the deficit should be corrected.

Like all other oral antiarrhythmics, TONOCARD has been reported to increase arrhythmias in some patients (see ADVERSE REACTIONS).

Information for Patients

Patients should be instructed to promptly report the development of bruising or bleeding; any signs of infections such as fever, chills, sore throat, or soreness and ulcers in the mouth; any pulmonary symptoms, such as exertional dyspnea, cough, or wheezing; rash.

Laboratory Tests

As with other antiarrhythmics, abnormal liver function tests, particularly in the early stages of therapy, have been reported. Periodic monitoring of liver function should be considered. Hepatitis and jaundice have been reported in some patients.

Drug Interactions

Tocainide and lidocaine are pharmacodynamically similar. The concomitant use of these two agents may cause an increased incidence of adverse reactions, including central nervous system adverse reactions such as seizure.

Specific interaction studies with cimetidine, digoxin, metoprolol, and warfarin have been conducted; no clinically significant interaction was seen with cimetidine, digoxin, or warfarin; but tocainide and metoprolol had additive effects on wedge pressure and cardiac index. TONOCARD has also been used in open studies with digitalis, beta-blocking agents, other antiarrhythmic agents, anticoagulants, and diuretics without evidence of clinically significant interactions. Nevertheless, caution should be exercised in the use of multiple drug therapy.

Pregnancy

Pregnancy Category C. In a teratogenicity study in rabbits, tocainide was administered orally at doses of 25, 50, and 100 mg/kg/day (about 1 to 4 times the usual human dose). No evidence of a drug-related teratogenic effect was noted; however, these doses were maternotoxic and produced a dose-related increase in abortions and stillbirths. In a teratogenicity study in rats, an oral dose of 300 mg/kg/day (about 12 times the usual human dose) showed no evidence of treatment-related fetal malformations, but maternotoxicity and an increase in fetal resorptions were noted. An oral dose of 30 mg/kg/day (about twice the usual human dose) did not produce any adverse effects.

In reproduction studies in rats at maternotoxic oral doses of 200 and 300 mg/kg/day (about 8 and 12 times the usual human dose, respectively), dystocia, and delayed parturition occurred which was accompanied by an increase in stillbirths and decreased survival in offspring during the first week postpartum. Growth and viability of surviving offspring were not affected for the remainder of the lactation period.

There are no adequate and well-controlled studies in pregnant women. TONOCARD should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether tocainide is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from TONOCARD, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

TONOCARD commonly produces minor, transient nervous system and gastrointestinal adverse reactions, but is otherwise generally well tolerated. TONOCARD has been evaluated in both short-term (n = 1,358) and long-term (n = 262) controlled studies as well as a compassionate use program. Dosages were lower in most of the controlled studies (1200 mg/day) and higher in the compassionate use program (1800 mg and more). In long-term (2-6 months) controlled studies, the most frequent adverse reactions were dizziness/vertigo (15.3 percent), nausea (14.5 percent), paresthesia (9.2 percent), and tremor (8.4 percent). These reactions were generally mild, transient, dose-related and reversible with a reduction in dosage, by

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taking the drug with food, or by therapy discontinuation. Tremor, when present, may be useful as a clinical indicator that the maximum dose is being approached. Adverse reactions leading to therapy discontinuation occurred in 21 percent of patients in long-term controlled trials and were usually related to the nervous system or digestive system.

Adverse reactions occurring in greater than one percent of patients from the short-term and long-term controlled studies appear in the following table:

	Percent of Patients Controlled Studies	
	Short-term (n = 1,358)	Long-term (n = 262)
BODY AS A WHOLE		
Tiredness/drowsiness/fatigue/lethargy/lassitude/sleepiness	1.6	0.8
Hot/cold feelings	0.5	1.5
CARDIOVASCULAR		
Hypotension	3.4	2.7
Bradycardia	1.8	0.4
Palpitations	1.8	0.4
Chest pain	1.6	0.4
Conduction disorders	1.5	0.0
Left ventricular failure	1.4	0.0
DIGESTIVE		
Nausea	15.2	14.5
Vomiting	8.3	4.6
Anorexia	1.2	1.9
Diarrhea/loose stools	0.0	3.8
NERVOUS SYSTEM/PSYCHIATRIC		
Dizziness/vertigo	8.0	15.3
Paresthesia	3.5	9.2
Tremor	2.9	8.4
Confusion/disorientation/hallucinations	2.1	2.7
Headache	2.1	4.6
Nervousness	1.5	0.4
Altered mood/awareness	1.5	3.4
Incoordination/unsteadiness/walking disturbances	1.2	0.0
Anxiety	1.1	1.5
Ataxia	0.2	3.0
SKIN		
Diaphoresis	5.1	2.3
Rash/skin lesion	0.4	8.4
SPECIAL SENSES		
Blurred vision/visual disturbances	1.3	1.5
Tinnitus/hearing loss	0.4	1.5
Nystagmus	0.0	1.1

An additional group of about 2,000 patients has been treated in a program allowing for the use of TONOCARD under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy, and comparatively high doses of TONOCARD were used. Fifty-four percent of the patients continued in the program for one year or longer, and 12 percent were treated for longer than three years, with the longest duration of therapy being nine years. Adverse reactions leading to therapy discontinuation occurred in 12 percent of patients (usually central nervous system effects or rash). A tabulation of adverse reactions occurring in one percent or more of patients follows:

	Percent of Patients Compassionate Use (n = 1,927)
CARDIOVASCULAR	
Increased ventricular arrhythmias/PVCs	10.9
CHF/progression of CHF	4.0
Tachycardia	3.2
Hypotension	1.8
Conduction disorders	1.3
Bradycardia	1.0
DIGESTIVE	
Nausea	24.6
Anorexia	11.3
Vomiting	9.0
Diarrhea/loose stools	6.8
MUSCULOSKELETAL	
Arthritis/arthralgia	4.7
Myalgia	1.7
NERVOUS SYSTEM/PSYCHIATRIC	
Dizziness/vertigo	25.3
Tremor	21.6
Nervousness	11.5
Confusion/disorientation/hallucinations	11.2
Altered mood/awareness	11.0
Ataxia	10.8
Paresthesia	9.2

TONOCARD® (Tocainide HCl|MSD)

	Percent of Patients Compassionate Use (n = 1,927)
SKIN	
Rash/skin lesion	12.2
Diaphoresis	8.3
Lupus	1.6
SPECIAL SENSES	
Blurred vision/vision disturbances	10.0
Nystagmus	1.1

Adverse reactions occurring in less than one percent of patients in either the controlled studies or the compassionate use program or since the drug was marketed are as follows:

Body as a Whole: Septicemia; septic shock; syncope; vaso-vagal episodes; edema; fever; chills; cinchonism; asthenia; malaise.

Cardiovascular: Ventricular fibrillation; extension of acute myocardial infarction; cardiogenic shock; pulmonary embolism; angina; AV block; hypertension; claudication; increased QRS duration; pleurisy/pericarditis; prolonged QT interval; right bundle branch block; cardiomegaly; sinus arrest; vasculitis; orthostatic hypotension; cold extremities.

Digestive: Hepatitis, jaundice (see PRECAUTIONS), abnormal liver function tests; pancreatitis; abdominal pain/discomfort; constipation; dysphagia; gastrointestinal symptoms (including dyspepsia); stomatitis; dry mouth; thirst.

Hematologic: Agranulocytosis; bone marrow depression; hypoplastic anemia; hemolytic anemia; anemia; leukopenia; neutropenia; thrombocytopenia; eosinophilia.

Metabolic and Immune: Hypersensitivity Reaction (including some of the following symptoms or signs: rash, fever, joint pains, abnormal liver function tests, eosinophilia); increased ANA.

Musculoskeletal: Muscle cramps; muscle twitching/spasm; neck pain; pain radiating from neck; pressure on shoulder.

Nervous System/Psychiatric: Coma; convulsions/seizures; myasthenia gravis; depression; psychosis; psychic disturbances; agitation; decreased mental acuity; dysarthria; impaired memory; increased stuttering/slurred speech; insomnia/sleeping disturbances; local anesthesia; dream abnormalities.

Respiratory: Respiratory arrest; pulmonary edema; pulmonary fibrosis; fibrosing alveolitis; pneumonia; interstitial pneumonitis; dyspnea; hiccough; yawning.

Skin: Stevens-Johnson syndrome; exfoliative dermatitis; erythema multiforme; urticaria; alopecia; pruritus; pallor/flushed face.

Special Senses: Diplopia; earache; taste perversion/smell perversion.

Urogenital: Urinary retention; polyuria/increased diuresis.

Agranulocytosis, bone marrow depression, leukopenia, neutropenia, hypoplastic anemia, and thrombocytopenia have been reported (0.18 percent) in patients receiving TONOCARD in controlled trials and the compassionate use program. Most of these events have been noted during the first 12 weeks of therapy. (See WARNINGS.)

Pulmonary fibrosis, interstitial pneumonitis, fibrosing alveolitis, pulmonary edema, and pneumonia, possibly drug related, have been reported in patients receiving TONOCARD. The incidence of pulmonary fibrosis (including interstitial pneumonitis and fibrosing alveolitis) was 0.11 percent in controlled trials and the compassionate use program. These events usually occurred in seriously ill patients. Symptoms of these pulmonary disorders and/or x-ray changes usually occurred following 3-18 weeks of therapy and two patients died. (See PRECAUTIONS.)

A number of disorders, in which a causal relationship with TONOCARD has not been established, have been reported in seriously ill patients. These include: renal failure, renal dysfunction, myocardial infarction, cerebrovascular accidents, and transient ischemic attacks. These disorders may be related to the patient's underlying condition.

HOW SUPPLIED

Scored tablets containing 400 mg or 600 mg in bottles of 100 and unit-dose packages of 100.

For more detailed information, consult your MSD Representative and the Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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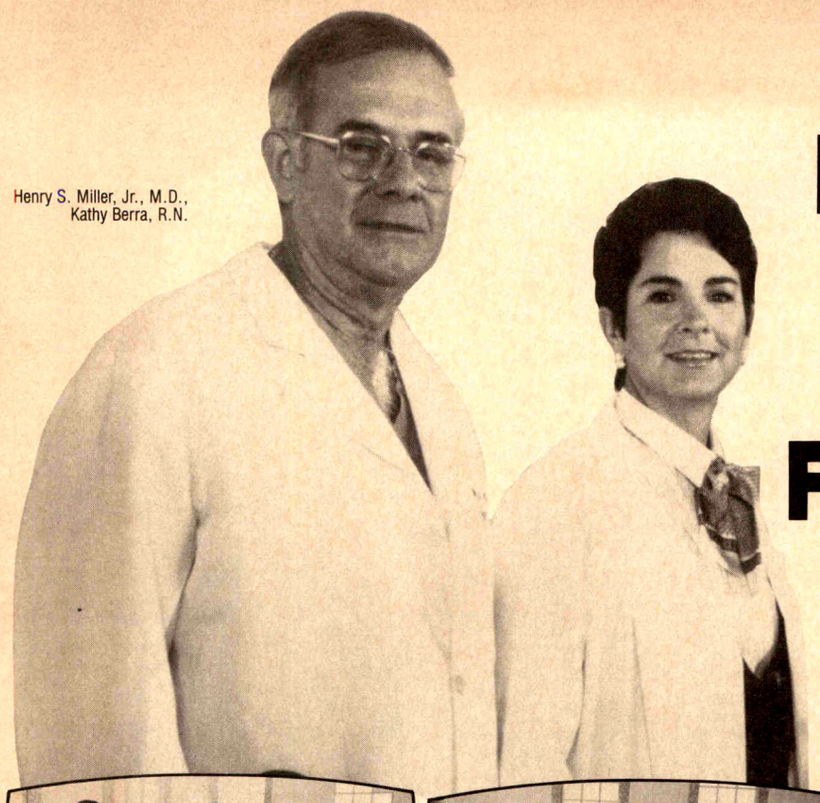

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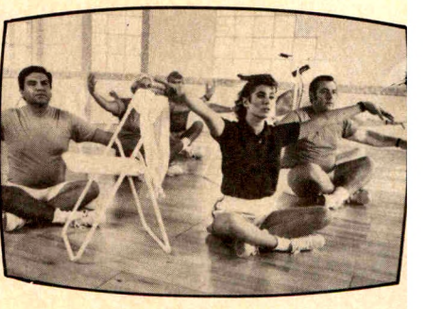

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PRODUCT INFORMATION

NORMODYNE®

brand of labetalol hydrochloride

Tablets

BRIEF SUMMARY

INDICATIONS AND USAGE

NORMODYNE (labetalol HCl) Tablets are indicated in the management of hypertension. NORMODYNE Tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS

NORMODYNE (labetalol HCl) Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS

Cardiac Failure Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered NORMODYNE (labetalol HCl), particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue NORMODYNE (labetalol HCl) therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema) Patients with bronchospastic disease should, in general, not receive beta-blockers. NORMODYNE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if NORMODYNE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions**).

PRECAUTIONS

General *Impaired Hepatic Function* NORMODYNE (labetalol HCl) Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with NORMODYNE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests

As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions

In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE Tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of NORMODYNE (labetalol HCl) Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8 to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol HCl, placebo, metoprolol and propranolol, over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

	Labetalol HCl (N = 227) %	Placebo (N = 98) %	Propranolol (N = 84) %	Metoprolol (N = 49) %
Body as a whole				
fatigue	5	0	12	12
asthenia	1	1	1	0
headache	2	1	1	2
Gastrointestinal				
nausea	6	1	1	2
vomiting	<1	0	0	0
dyspepsia	3	1	1	0
abdominal pain	0	0	1	2
diarrhea	<1	0	2	0
taste distortion	1	0	0	0
Central and Peripheral Nervous Systems				
dizziness	11	3	4	4
paresthesias	<1	0	0	0
drowsiness	<1	2	2	2
Autonomic Nervous System				
nasal stuffiness	3	0	0	0
ejaculation failure	2	0	0	0
impotence	1	0	1	3
increased sweating	<1	0	0	0
Cardiovascular				
edema	1	0	0	0
postural hypotension	1	0	0	0
bradycardia	0	0	5	12
Respiratory				
dyspnea	2	0	1	2
Skin				
rash	1	0	0	0
Special Senses				
vision abnormality	1	0	0	0
vertigo	2	1	0	0

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e., a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

Labetalol HCl Daily Dose (mg)	200	300	400	600
Number of Patients	522	181	606	608
Dizziness (%)	2	3	3	3
Fatigue	2	1	4	4
Nausea	<1	0	1	2
Vomiting	0	0	<1	<1
Dyspepsia	1	0	2	1
Paresthesias	2	0	2	2
Nasal Stuffiness	1	1	2	2
Ejaculation Failure	0	2	1	2
Impotence	1	1	1	1
Edema	1	0	1	1

Labetalol HCl Daily Dose (mg)	800	900	1200	1600	2400
Number of Patients	503	117	411	242	175
Dizziness (%)	5	1	9	13	16
Fatigue	5	3	7	6	10
Nausea	4	0	7	11	19
Vomiting	<1	0	1	2	3
Dyspepsia	1	0	2	2	4

Labetalol HCl Daily Dose (mg) (cont.)	800	900	1200	1600	2400
Paresthesias	1	1	2	5	5
Nasal Stuffiness	2	2	4	5	6
Ejaculation Failure	3	0	4	3	5
Impotence	2	4	3	4	3
Edema	1	0	1	2	2

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular Postural hypotension, including rarely, syncope.

Central and Peripheral Nervous Systems Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and usually occurred at the beginning of treatment.

Collagen Disorders Systemic lupus erythematosus; positive antinuclear factor (ANF).

Eyes Dry eyes.

Immunological System Antimitochondrial antibodies.

Liver and Biliary System Cholestasis with or without jaundice.

Musculo-Skeletal System Muscle cramps; toxic myopathy.

Respiratory System Bronchospasm.

Skin and Appendages Rashes of various types, such as generalized maculo-papular; lichenoid; urticarial; bullous lichen planus; psoriaform; facial erythema; Peyronie's disease; reversible alopecia.

Urinary System Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects

In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents.

Central Nervous System Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular Intensification of AV block. See **CONTRAINDICATIONS.**

Allergic Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal Mesenteric artery thrombosis; ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical laboratory tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE

Overdosage with NORMODYNE (labetalol HCl) Tablets causes excessive hypotension which is posture sensitive, and sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: *Excessive bradycardia* — administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. *Cardiac failure* — administer a digitalis glycoside and a diuretic. *Hypotension* — administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm* — administer a $beta_2$-stimulating agent and/or a theophylline preparation.

Gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 gm/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual maintenance dosage of labetalol HCl is between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol HCl is usually seen within the first one to three hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered bid, the same total daily dose administered three times daily may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg twice daily.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of NORMODYNE Tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, NORMODYNE Tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

HOW SUPPLIED

NORMODYNE (labetalol HCl) Tablets, 100 mg, light-brown, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 244, and on the other side the number 100 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0244-04), 500 (NDC-0085-0244-05), and box of 100 for unit-dose dispensing (NDC-0085-0244-08).

NORMODYNE (labetalol HCl) Tablets, 200 mg, white, round, scored, film-coated tablets engraved on one side with Schering and product identification numbers 752, and on the other side the number 200 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0752-04), 500 (NDC-0085-0752-05), box of 100 for unit-dose dispensing (NDC-0085-0752-08), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0752-03).

NORMODYNE (labetalol HCl) Tablets, 300 mg, blue, round, film-coated tablets engraved on one side with Schering and product identification numbers 438, and on the other side the number 300 for the strength and "NORMODYNE"; bottles of 100 (NDC-0085-0438-03), 500 (NDC-0085-0438-05), box of 100 for unit-dose dispensing (NDC-0085-0438-06), and Patient Calendar Package of 56 (4 bottles of 14 tablets) (NDC-0085-0438-02).

NORMODYNE (labetalol HCl) Tablets should be stored between 2° and 30°C (36° and 86°F).

NORMODYNE (labetalol HCl) Tablets in the unit-dose boxes should be protected from excessive moisture.

For complete prescribing information, please consult package insert.

Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033 USA

Revised 3/85

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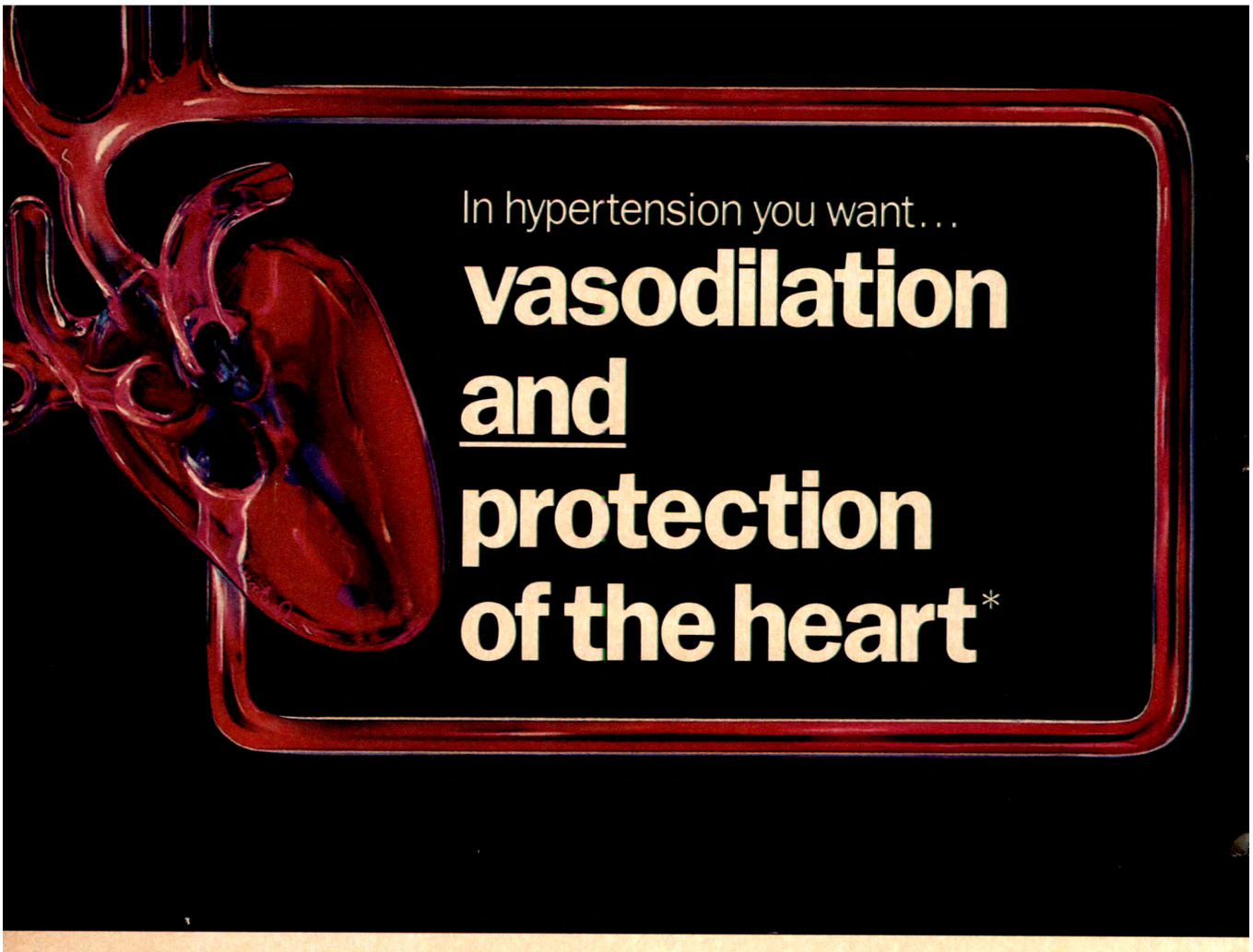

NORMODYNE® gives you both
(labetalol HCl) Tablets

	vasodilation	beta blockade
NORMODYNE (labetalol HCl) Tablets	✓	✓
Beta Blockers		✓
ACE Inhibitors	✓	
Calcium Channel Blockers	✓	

- ☐ Low incidence of impotence, fatigue, or cold extremities†
- ☐ Lipid and potassium levels are not adversely affected
- ☐ Minimizes risk of reflex tachycardia
- ☐ Maintains cardiac output
- ☐ Maintains exercise capacity
- ☐ Does not adversely affect heart rate
- ☐ Maintains blood flow to vital organs
- ☐ Renal function is unimpaired

*reduces double product (HR × SBP) and minimizes the risk of reflex tachycardia

†Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, the most common side effects noted in treating mild to moderate hypertension with NORMODYNE (labetalol HCl) Tablets include dizziness (11%), nausea (6%), and fatigue (5%). Dyspepsia (3%), nasal stuffiness (3%), impotence (1%), and drowsiness (<1%) occurred to a lesser degree. Overall, reports of symptomatic postural hypotension have been uncommon and have included rare instances of syncope. For complete side effects profile, see Prescribing Information.

For Brief Summary, please see reverse side of page.

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826 Angina Pectoris and Coronary Artery Disease in Severe Aortic Regurgitation

Philippe Timmermans, Jos L. Willems, Jan Piessens, and Hilaire De Geest

A consecutive series of 198 patients (148 men and 50 women) with pure, isolated, severe aortic regurgitation was retrospectively studied to determine the prevalence of angiographically significant coronary artery disease (CAD) and its relation to angina pectoris and coronary risk factors. Significant CAD (coronary diameter stenoses >50%) was found in 28 cases (14%). Typical angina was present in 18% and atypical chest pain in 16%. Angina alone had a sensitivity of 57% to detect significant CAD. By using multivariate logistic regression, a risk score could be calculated that increased the sensitivity to 74% at equal specificity. Almost 40% had a risk score of <-2.9 (only 1 patient in this group had CAD). It is concluded that coronary arteriography can safely be omitted in many patients with severe aortic regurgitation if they have no symptoms of myocardial ischemia or risk factors known to increase its incidence.

CARDIOMYOPATHY

830 Relation Between Serum Nifedipine Concentration and Hemodynamic Effects in Nonobstructive Hypertrophic Cardiomyopathy

Sandro Betocchi, Robert O. Bonow, Richard O. Cannon, III, Lawrence J. Lesko, Harold G. Ostrow, Rita M. Watson, and Douglas R. Rosing

The relation between the hemodynamic effects of sublingual nifedipine and nifedipine concentration was studied in 13 patients with nonobstructive hypertrophic cardiomyopathy (HC) during cardiac catheterization. Nifedipine resulted in reduced peripheral vascular resistance which correlated with drug concentration ($r = -0.63$), associated with increased heart rate and cardiac index. At low to medium drug concentrations ($\leq$120 ng/ml), these peripheral effects predominated, with increased left ventricular (LV) stroke volume and increased ejection fraction, with no change in the end-systolic pressure-volume relation and no change in pulmonary artery wedge pressure. However, at high concentrations (>120 ng/ml), negative inotropic effects predominated; despite greater reduction in peripheral resistance at these concentrations, stroke volume index decreased, both end-systolic and end-diastolic volumes increased, ejection fraction decreased and LV end-diastolic and pulmonary artery wedge pressures increased. Thus, low to medium concentrations of nifedipine augment LV ejection performance in nonobstructive HC, whereas high concentrations result in deleterious negative inotropic effects.

836 A Comparative Study of Thallium-201 Single-Photon Emission Computed Tomography and Electrocardiography in Duchenne and Other Types of Muscular Dystrophy

Shuhei Yamamoto, Hideo Matsushima, Akio Suzuki, Iwao Sotobata, Toshikatsu Indo, and Yukihiko Matsuoka

We compared thallium-201 single-photon emission computed tomography (SPECT) with electrocardiography in 47 patients with Duchenne, facioscapulohumeral, limb-girdle and myotonic dystrophies. SPECT showed (multiple) hypoperfusion (37 patients), malrotation (23), apical aneurysm (5) and dilatation (7) of the left ventricle. Electrocardiography frequently showed QRS wave abnormalities (36 patients). In the Du-

chenne type, SPECT hypoperfusion and QRS abnormalities were frequent in the posteroapical and the posterolateral walls, respectively. Both were scattered over the left ventricle in the 3 other types. In this disease, SPECT hypoperfusion was often shown despite minimal electrocardiographic changes and irrespective of clinical subtype and skeletal involvement.

CONGENITAL HEART DISEASE

844 Doppler Ultrasound Evaluation of Valvar Pulmonary Stenosis from Multiple Transducer Positions in Children Requiring Pulmonary Valvuloplasty

Elman G. Frantz and Norman H. Silverman

This study compares the estimates of peak pressure difference in children with valvar pulmonary stenosis admitted for valvuloplasty with continuous wave Doppler ultrasound using the modified Bernoulli equation from several different transducer positions. Because jet direction varies from the axial direction of normal pulmonary flow, only an appropriate alignment of the ultrasound will determine the highest velocity signal. We examined whether the conventional parasternal transducer position or an alternate transducer from the subcostal, suprasternal or apical transducer position produced the highest velocity signals in 24 children. In 12 of these children (50%) studied prior to, and in 8 (67%) studied during cardiac catheterization, a higher velocity was recorded from a nonparasternal position. The same transducer position produced the highest velocity after as it did before valvuloplasty although the numbers are too small to generalize. The study shows that in valvar pulmonary stenosis multiple transducer positions are required to determine peak transpulmonary velocity.

850 Anomalous Origin of a Pulmonary Artery from the Ascending Aorta: Associated Anomalies and Pathogenesis

Lynn M. Kutsche and L.H.S. Van Mierop

The pathologic anatomic features and associated cardiovascular anomalies of 99 cases of anomalous origin of 1 pulmonary artery from the aorta were analyzed. Anomalous origin of the right pulmonary artery (PA) was more common than that of the left PA. An anomalous right PA usually arose from the posterior aspect of the ascending aorta close to the aortic valve. Less commonly, it originated near the innominate artery. Patent ductus arteriosus and aorticopulmonary septal defect were common in anomalous origin of the right PA. Tetralogy of Fallot, aortic arch anomalies or both were always present in anomalous origin of the left PA. An association with DiGeorge syndrome was not seen. Anomalous origin of the right PA and anomalous origin of the left PA appear to be unrelated to each other pathogenetically. Moreover, the distal type of anomalous origin of the right PA appears to be pathogenetically distinct from that which arises close to the aortic valve. These pathogenetic relations should be considered in epidemiologic studies of congenital heart disease.

Continued on page A76

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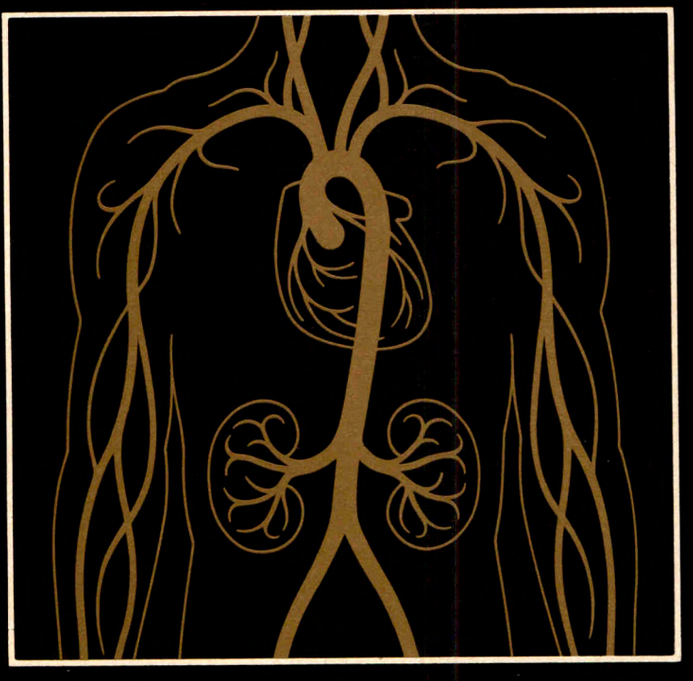

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BRIEF SUMMARY

Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure<90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present).
Warnings: Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction<30%) or moderate to severe symptoms of cardiac failure and in patients with significant ventricular dysfunction if they are receiving a beta-adrenergic blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce a decrease in blood pressure below normal levels, which may result in dizziness or symptomatic hypotension. Elevations of liver enzymes have been reported. Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). The effect of verapamil on AV conduction and the SA node may cause asymptomatic 1st-degree AV block and transient bradycardia, sometimes with nodal escape rhythms. PR-interval prolongation is correlated with verapamil plasma concentrations especially during initial titration. Higher degrees of AV block are infrequent (0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.
Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Studies in a small number of patients suggest that concomitant use of Calan and oral beta-adrenergic blockers may be beneficial in certain patients with chronic stable angina or hypertension. Combined therapy can also have adverse effects on cardiac function; therefore patients should be closely monitored. A decrease in metoprolol clearance may occur with concurrent use of verapamil and metoprolol. Chronic verapamil treatment increases serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient reassessed. Verapamil used concomitantly with oral antihypertensive agents will usually have an additive effect on lowering blood pressure that in some cases may be excessive; therefore patients should be monitored appropriately. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Quinidine levels may increase during verapamil therapy. Clearance of verapamil may be reduced in concomitant use with cimetidine. Concomitant use of verapamil and lithium may result in decreased serum lithium levels. Verapamil therapy may increase carbamazepine concentrations during combined use. Therapy with rifampin may markedly reduce oral verapamil bioavailability. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Another study in rats showed no evidence of carcinogenicity. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy in children under 18 have not been established.
Adverse Reactions— oral verapamil: Constipation (8.4%), dizziness (3.5%), nausea (2.7%), hypotension (2.5%), edema (2.1%), headache (1.9%), CHF/pulmonary edema (1.8%), fatigue (1.7%), bradycardia: HR <50/min (1.4%), AV block: total 1°, 2°, 3° (1.3%)/3rd-degree (0.8%), flushing (0.1%); elevations of liver enzymes have been reported (see *Warnings*). The following reactions, reported in 1.0% or less of patients, occurred under circumstances where a causal relationship is not certain: angina pectoris, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, dyspnea, arthralgia, rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, blurred vision, gynecomastia, impotence, increased urination, spotty menstruation.

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857 **An Echocardiagraphic Study of the Association of Ventricular Septal Defect and Right Ventricular Muscle Bundles with a Fixed Subaortic Abnormality**

Michael Vogel, Jeffrey F. Smallhorn, Robert M. Freedom, John Coles, William G. Williams, and George A. Trusler

Since 1983, 36 patients with ventricular septal defect and anomalous right ventricular muscle bundles have been evaluated by cross-sectional echocardiography to address the incidence of an associated subaortic abnormality. Of these, 32 had an indentifiable subaortic abnormality. Surgical confirmation of the presence or absence of an abnormality was available in 26. A recordable Doppler gradient across the left ventricular outflow tract of ≥10 mm Hg was present only in 10. It appears that the incidence of a subaortic abnormality in this setting is far greater than previously suspected.

861 **Cardiorespiratory Exercise Testing After Venous Switch Operation in Children with Complete Transposition of the Great Arteries**

Tony Reybrouck, Monique Dumoulin, and Lucas G. Van der Hauwaert

In 14 children who underwent a venous switch operation, exercise testing was performed 3 to 15 years (mean 8) after the operation. Exercise performance capacity was assessed by the determination of the ventilatory threshold during exercise, defined as the highest exercise intensity before which hyperventilation starts during graded exercise. The mean ventilatory threshold (72 ± 15%) was significantly lower ($p < 0.01$) in these patients than the age-predicted normal mean value. A lower than normal heart rate response to exercise was observed in nearly half of the patients, and was not associated with a high or normal value for ventilatory threshold (as would be expected in endurance-trained subjects). This blunted heart rate response during exercise suggests sinoatrial dysfunction secondary to extensive intraatrial operation.

EDITORIALS

866 **Influence of Stenosis Severity on Coronary Collateral Development and Importance of Collaterals in Maintaining Left Ventricular Function During Acute Coronary Occlusion**

Stephen E. Epstein

869 **Left Axis Deviation and Left Anterior Fascicular Block**

David H. Spodick

871 **FROM THE EDITOR**

872 **CORRECTIONS**

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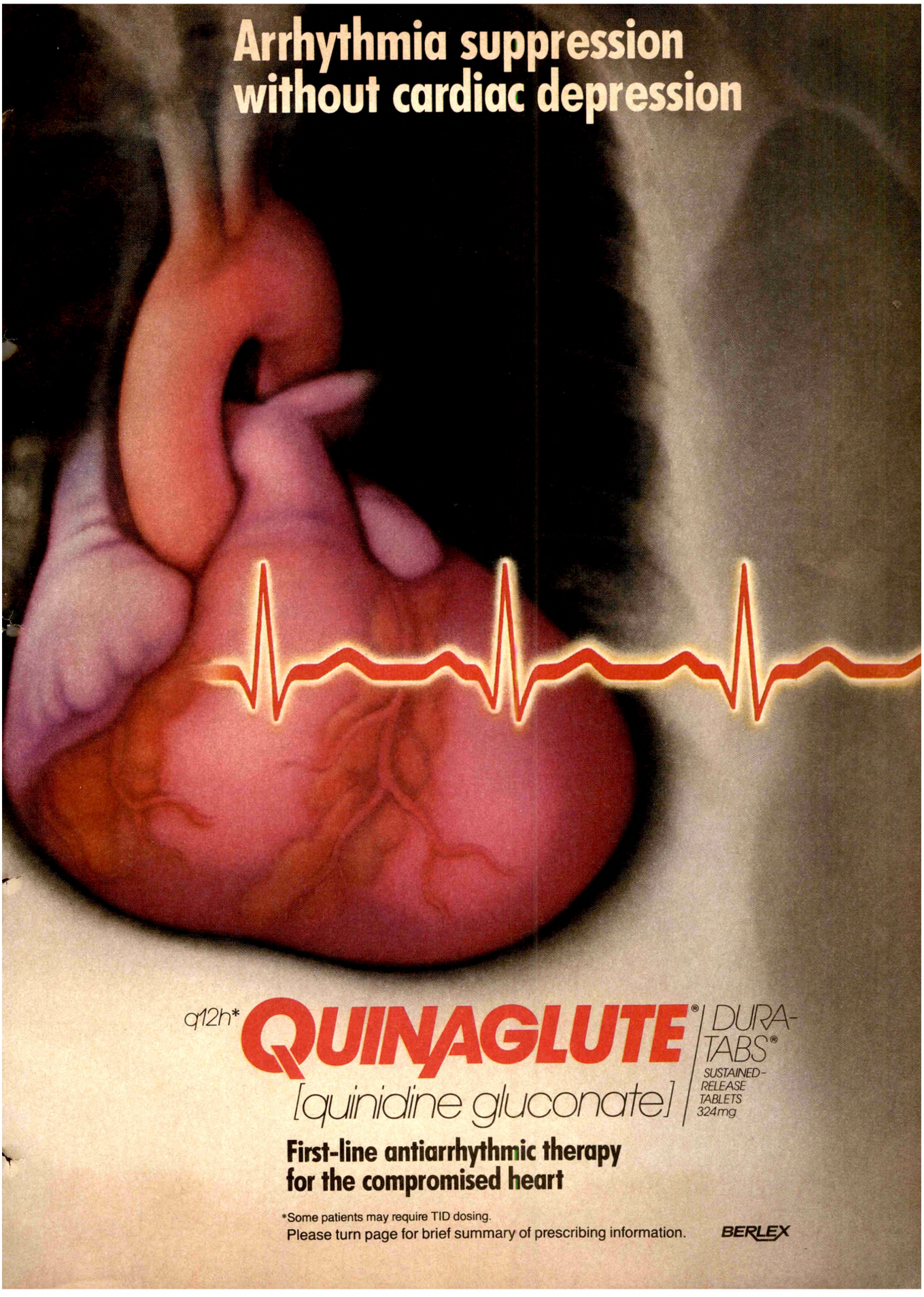
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INDICATIONS AND USAGE: QUINAGLUTE® (quinidine gluconate) DURA-TABS® sustained-release tablets are indicated in the prevention and/or treatment of:

1. Ventricular arrhythmias: Premature ventricular contractions, ventricular tachycardia (when not associated with complete heartblock).

2. Junctional (nodal) arrhythmias: A-V junctional premature complexes, paroxysmal junctional tachycardia. **3. Supraventricular (atrial) arrhythmias:** Premature atrial contractions, paroxysmal atrial tachycardia, atrial flutter, atrial fibrillation (chronic and paroxysmal).

CONTRAINDICATIONS: 1. Idiosyncrasy or hypersensitivity to quinidine. 2. Complete A-V block. 3. Complete bundle branch block or other severe intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. 4. Digitalis intoxication manifested by A-V conduction disorders. 5. Myasthenia gravis. 6. Aberrant impulses and abnormal rhythms due to escape mechanisms.

WARNINGS: 1. In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administation of quinidine.

2. Recent reports indicate that plasma concentrations of digoxin increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored. Reduction of digoxin dosage may have to be considered.

3. Manifestations of quinidine cardiotoxicity such as excessive prolongation of the Q-T interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

4. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function such as hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

5. Quinidine should be used with extreme caution in patients with incomplete A-V block since complete block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

6. Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in plasma leading to toxicity.

7. Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or plasma levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

8. A few cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported in patients taking quinidine. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4 to 8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

PRECAUTIONS: General: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate may be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and possible determination of plasma quinidine levels is indicated when large doses are used, or with patients who present an increased risk.

Information for Patients: As with all solid oral medications, QUINAGLUTE® DURA-TABS® tablets should be taken with an adequate amount of fluid, preferably in an upright position, to facilitate swallowing.

Drug Interactions: *Drug*	*Effect*
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Potential for reduction of quinidine plasma levels
Quinidine with cimetidine	Potential for elevation of quinidine plasma levels
Quinidine with digoxin	Increased plasma concentrations of digoxin (see WARNINGS)

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of quinidine. There is currently no evidence of quinidine-induced mutagenesis or impairment of fertility.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. QUINAGLUTE® DURA-TABS® tablets should be given to a pregnant woman only if clearly needed. *Nonteratogenic Effects:* Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers: Caution should be exercised when QUINAGLUTE® DURA-TABS® tablets are administered to a nursing woman due to passage of the drug into breast milk.

Pediatric Use: There are no adequate and well-controlled studies establishing the safety and effectiveness of QUINAGLUTE® DURA-TABS® tablets in children.

ADVERSE REACTIONS: Symptoms of cinchonism, ringing in ears, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal in nature. These gastrointestinal effects include nausea, vomiting, abdominal pain and diarrhea.

Less frequently encountered adverse reactions:

Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism and hypotension.

Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenia (purpura), agranulocytosis.

Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision field, photophobia, diplopia, night blindness, scotomata), optic neuritis.

Dermatologic: Rash, cutaneous flushing with intense pruritis, urticaria. Photosensitivity has also been reported.

Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatic toxicity, including granulomatous hepatitis (see WARNINGS). Although rare, there have been reports of lupus erythematosus in patients taking quinidine.

See package insert for full information. Rev. 11/85

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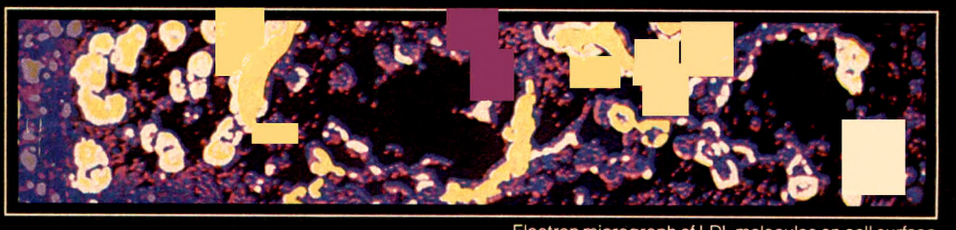

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CONTRAINDICATIONS: None known.

WARNINGS: MINIPRESS may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120–160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS. The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS therapy.

PRECAUTIONS: ***Information for Patients:*** Dizziness or drowsiness may occur after the first dose of this medicine. Avoid driving or performing hazardous tasks for the first 24 hours after taking this medicine or when the dose is increased. Dizziness, lightheadedness or fainting may occur, especially when rising from a lying or sitting position. Getting up slowly may help lessen the problem. These effects may also occur if you drink alcohol, stand for long periods of time, exercise, or if the weather is hot. While taking MINIPRESS, be careful in the amount of alcohol you drink. Also, use extra care during exercise or hot weather, or if standing for long periods. Check with your physician if you have any questions.

Drug Interactions: MINIPRESS has been administered without any adverse drug interaction in limited clinical experience to date with the following: (1) cardiac glycosides–digitalis and digoxin; (2) hypoglycemics–insulin, chlorpropamide, phenformin, tolazamide, and tolbutamide; (3) tranquilizers and sedatives–chlordiazepoxide, diazepam, and phenobarbital; (4) antigout–allopurinol, colchicine, and probenecid; (5) antiarrhythmics–procainamide, propranolol (see WARNINGS however), and quinidine; and (6) analgesics, antipyretics and anti-inflammatories–propoxyphene, aspirin, indomethacin, and phenylbutazone.

Addition of a diuretic or other antihypertensive agent to MINIPRESS has been shown to cause an additive hypotensive effect.

Drug/Laboratory Test Interactions: False positive results may occur in screening tests for pheochromocytoma in patients who are being treated with prazosin. If an elevated VMA is found, prazosin should be discontinued and the patient retested after a month.

Laboratory Tests: In clinical studies in which lipid profiles were followed, there were generally no adverse changes noted between pre- and post-treatment lipid levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenic potential was demonstrated in an 18 month study in rats with MINIPRESS (prazosin hydrochloride) at dose levels more than 225 times the usual maximum recommended human dose of 20 mg per day. MINIPRESS was not mutagenic in *in vivo* genetic toxicology studies. In a fertility and general reproductive performance study in rats, both males and females, treated with 75 mg/kg (225 times the usual maximum recommended human dose), demonstrated decreased fertility while those treated with 25 mg/kg (75 times the usual maximum recommended human dose) did not.

In chronic studies (one year or more) of MINIPRESS in rats and dogs, testicular changes consisting of atrophy and necrosis occurred at 25 mg/kg/day (75 times the usual maximum recommended human dose). No testicular changes were seen in rats or dogs at 10 mg/kg/day (30 times the usual maximum recommended human dose). In view of the testicular changes observed in animals, 105 patients on long term MINIPRESS therapy were monitored for 17-ketosteroid excretion and no changes indicating a drug effect were observed. In addition, 27 males on MINIPRESS for up to 51 months did not have changes in sperm morphology suggestive of drug effect.

Usage In Pregnancy: Pregnancy Category C. There are no adequate and well controlled studies which establish the safety of MINIPRESS (prazosin HCl) in pregnant women. MINIPRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers: MINIPRESS has been shown to be excreted in small amounts in human milk. Caution should be exercised when MINIPRESS is administered to a nursing woman.

Usage in Children: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Clinical trials were conducted on more than 900 patients. During these trials and subsequent marketing experience, the most frequent reactions associated with MINIPRESS therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

Less frequent adverse reactions which are reported to occur in 1–4% of patients are:

Gastrointestinal: vomiting, diarrhea, constipation; *Cardiovascular:* edema, orthostatic hypotension, dyspnea, syncope; *Central Nervous System:* vertigo, depression, nervousness; *Dermatologic:* rash; *Genitourinary:* urinary frequency; *EENT:* blurred vision, reddened sclera, epistaxis, dry mouth, nasal congestion.

In addition, fewer than 1% of patients have reported the following (in some instances, exact causal relationships have not been established):

Gastrointestinal: abdominal discomfort and/or pain, liver function abnormalities, pancreatitis; *Cardiovascular:* tachycardia; *Central Nervous System:* paresthesia, hallucinations; *Dermatologic:* pruritus, alopecia, lichen planus; *Genitourinary:* incontinence, impotence, priapism; *EENT:* tinnitus; *Other:* diaphoresis, fever.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported.

OVERDOSAGE: Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate MINIPRESS is not dialysable because it is protein bound.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS should be adjusted according to individual blood pressure response.

Initial Dose: 1 mg two or three times a day.

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy; however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

Revised November 1986

References: 1. Leren P, Helgeland A, Hjermann I, et al: The Oslo study: CHD risk factors, socioeconomic influences, and intervention. *Am Heart J* 106:1200-1206, 1983. **2.** Neusy A-J, Lowenstein J: Effects of prazosin, atenolol, and thiazide diuretic on plasma lipids in patients with essential hypertension. *Am J Med* 80(suppl 2A):94-99, 1986. **3.** Rouffy J, Jaillard J: Effects on lipids, lipoproteins, and apoproteins A and B of two antihypertensive agents: Prazosin and atenolol. *Am J Med* 80(suppl 2A):100-103, 1986. **4.** Ames RP, Hill P: Antihypertensive therapy and the risk of coronary heart disease. *J Cardiovasc Pharmacol* 4(suppl 2):206-212, 1982. **5.** Pitts NE: The clinical evaluation of prazosin, a new antihypertensive agent, in *Prazosin Clinical Symposium Proceedings*. Published as a special report by *Postgraduate Medicine: Custom Communications*, New York, McGraw-Hill Co, 1975, pp 117-127. **6.** Ames RP: Negative effects of diuretic drugs on metabolic risk factors for coronary heart disease: Possible alternative drug therapies. *Am J Cardiol* 51:632-638, 1983. **7.** Leichter SB, Baumgardner B: Effects of chronic prazosin therapy on intermediary metabolism in diabetic patients. *J Cardiovasc Med* (special suppl):38-42, 1981. **8.** Okun R: Effectiveness of prazosin as initial antihypertensive therapy. *Am J Cardiol* 51(special suppl):644-650, 1983. **9.** Sandor FF, Pickens PT, Crallan J: Variations of plasma potassium concentrations during long-term treatment of hypertension with diuretics without potassium supplements. *Br Med J* 284:711-715, 1982. **10.** Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. Report of Medical Research Council Working Party on mild to moderate hypertension. *Lancet* pp 539-543, September 12, 1981.

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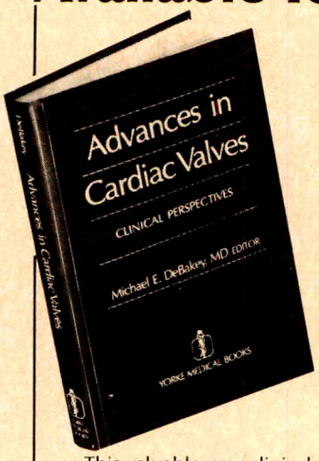

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edited by
Michael E. DeBakey, MD

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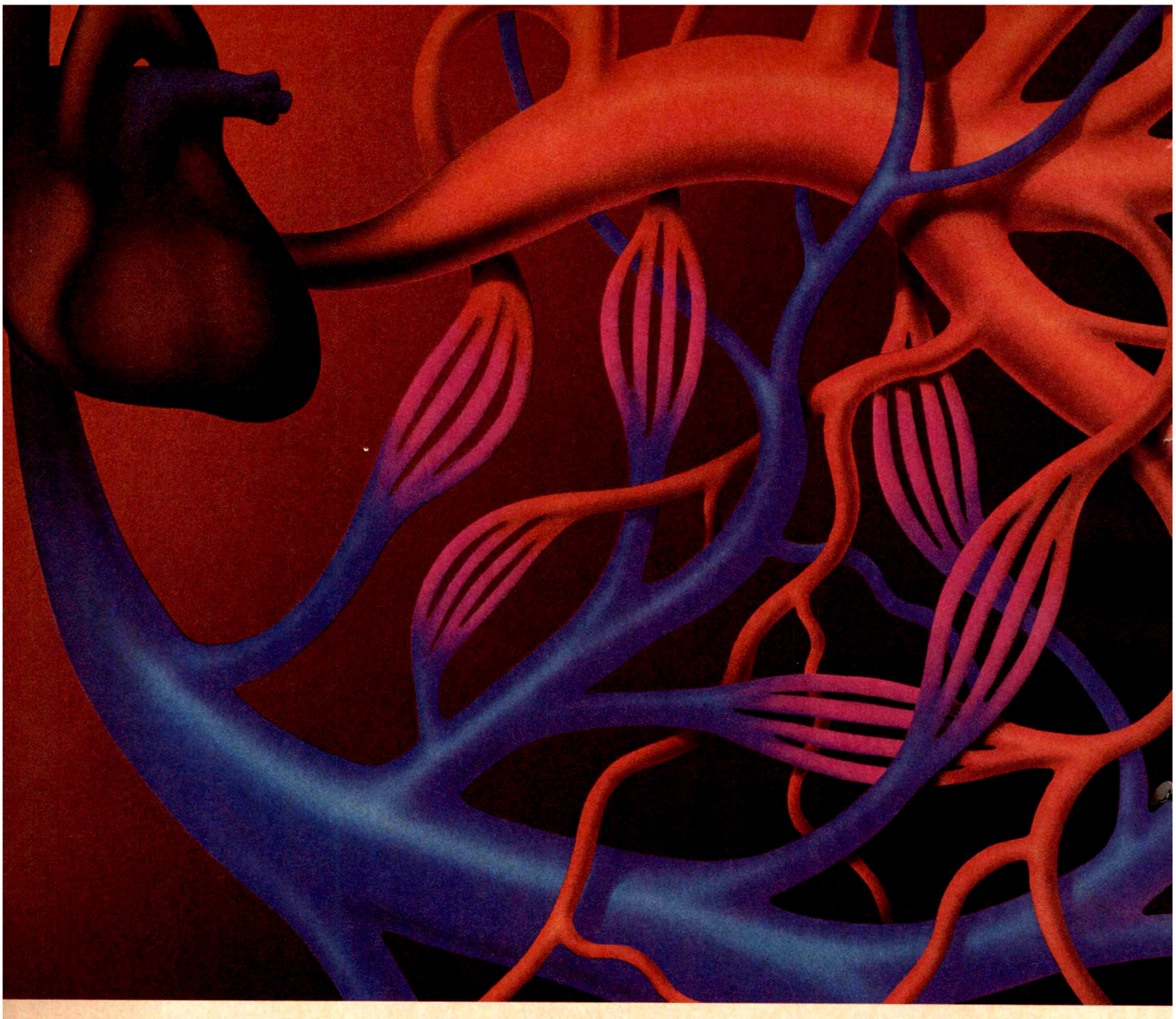

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VOLUME 61

NUMBER 10

CORONARY ARTERY DISEASE

Determinants and Protective Potential of Coronary Arterial Collaterals as Assessed by an Angioplasty Model

K. PETER RENTROP, MD, JOHN C. THORNTON, PhD, FREDERICK FEIT, MD, and MARK VAN BUSKIRK, MS

Two indexes of collateral blood flow, the ratio of distal coronary occlusion pressure/aortic pressure (DCOP/Pao) and angiographic collateral class were determined during elective angioplasty in 36 patients with normal left ventricular function. The association between collateral indexes and 8 anatomic and clinical variables was assessed. A reduction in luminal diameter by ≥70% predicted angiographically demonstrable collaterals with 100% specificity and 85% sensitivity. Lesion severity (stenosis) correlated with both collateral class and DCOP/Pao: DCOP/Pao = 2.8809 − 0.0729 × stenosis + 0.00049 × stenosis^2. The data suggest a quantitative relation between lesion severity and collateral development beyond a threshold value of 70% stenosis. Left ventricular ejection fraction during ischemia caused by balloon occlusion (EFo) was found to be primarily determined by lesion location; however, collateral flow modified EFo significantly. For mid-left anterior descending and right coronary artery: EFo = 59 + 26 × (DCOP/Pao); for proximal left anterior descending artery: EFo = 24 + 89 × (DCOP/Pao). A model predicting the hemodynamic and clinical consequences of abrupt coronary closure based on lesion location and severity was developed. In the second study phase, this model was tested retrospectively in a different group of 23 patients who experienced coronary occlusion as a complication of angioplasty. The data of both study phases suggest that left ventricular function and clinical outcome after abrupt coronary closure are determined by an interaction between location of the coronary artery obstruction and the amount of collateral flow. Lesion severity and the extent of functional impairment resulting from abrupt coronary closure are inversely related.

(Am J Cardiol 1988;61:677–684)

Human hearts have <100-μ diameter congenital collateral channels, which can enlarge in the presence of a critical coronary lesion.[1-6] A quantitative relation between collateral development and the factors that might promote it—including lesion severity—has not been established. The functional relevance of collaterals in humans who experience abrupt coronary closure is controversial. In previous studies the relation between the degree of collateralization and the extent of myocardial necrosis[1,3] or wall motion abnormality[7,10] has been assessed days or weeks following coronary closure. In the experimental animal abrupt coro-

nary closure has been found to cause an increase of tangential wall stress in collaterals leading to a rapid luminal expansion of these channels.[11] After 24 hours there was mitotic activity resulting in active collateral growth.[12] Thus, the degree of collateralization at the time of acute coronary closure may be less than that found days or weeks after the event. Contradictory results of prior human studies may be explained by their retrospective nature.

With the development of coronary angioplasty it became possible to determine the immediate consequences of abrupt coronary closure in humans with simultaneous assessment of indexes of collateral flow. Two such indexes can be determined during controlled obstruction of a coronary artery by the inflated balloon used in percutaneous transluminal coronary angioplasty: distal coronary occlusion pressure and degree of angiographic visualization of collaterals.[13] Both indexes have been found to correlate with the amount of retrograde coronary blood flow determined during coronary artery bypass surgery.[14] In the animal model, coronary occlusion pressure is an accepted index of collateral flow.[15-17] In the present study, the association between indexes of collateral flow and lesion severity (as well as clinical variables) was assessed. Furthermore, the indexes of collateral flow were correlated with ejection fraction determined during angioplasty. Two models were developed to predict the degree of impairment of left ventricular function after abrupt coronary closure based on variables determined before or during angioplasty. In phase II, 1 of these models was validated clinically.

From St. Vincent's, Mount Sinai and New York University Medical Centers, New York, New York. This study was supported by a grant from The Foundation for Interventional Cardiology, Inc., New York, New York. Manuscript received September 30, 1987; revised manuscript received and accepted December 4, 1987.

Address for reprints: K. Peter Rentrop, MD, Reid Building, 4th Floor, 350 Boulevard, Passaic, New Jersey 07055.

Methods

Phase I. Development of the model: Thirty-six patients who had successful elective angioplasty for 1-vessel disease of the left anterior descending or right coronary artery comprise the study population. Exclusion criteria have been published previously.[13] Informed consent was obtained from all patients. The consequences of abrupt coronary closure were assessed in the 29 patients whose coronary artery obstruction was not complete at baseline. Baseline ejection fraction was normal in all patients included in this portion of the study.

Cardiac catheterization and angioplasty: Patients were premedicated with oxazepam, 2 mg intramuscularly and 2 mg orally; aspirin, 325 mg orally; dipyridamole, 75 mg orally; nifedipine, 10 mg sublingually. Nitroglycerin was administered via a continuous intravenous infusion to maintain a systolic blood pressure between 105 and 120 mm Hg. Coronary angioplasty was performed using a standard brachial or femoral approach. A second arterial access was gained by placing a 5Fr sheath percutaneously in a femoral artery. Heparin sulfate, 10,000 units was administered intraarterially. Angioplasty was performed with standard, double lumen balloon catheters (USCI, ACS), en-

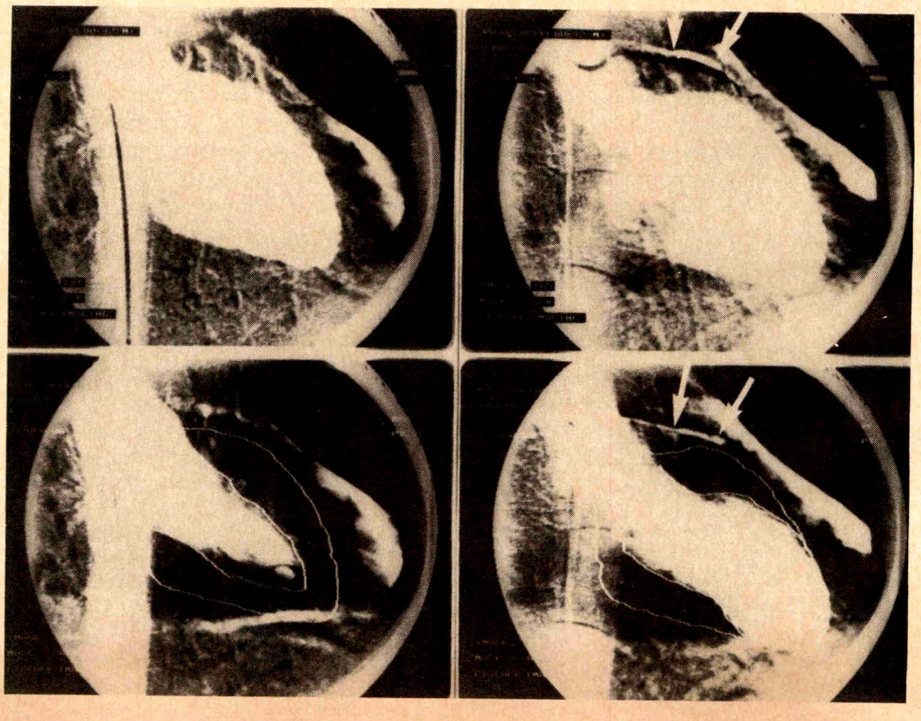

FIGURE 1. Digital subtraction ventriculograms at baseline (*left*) and during balloon inflation (*right*) in a study patient. The end-diastolic frames correspond to the upper panel and the end-systolic frames to the lower panel. The inflated balloon in the left anterior descending artery is indicated by *arrows*. Calculation of ejection fraction is based on the computer-generated outlines of the end-diastolic and end-systolic silhouettes (*lower frames*).

TABLE I Distribution of Baseline Variables by Collateral Class

	Collateral Class			
	0 (n = 7)	I (n = 14)	II (n = 8)	III (n = 7)
Age (yrs)	49 ± 9	56 ± 5	54 ± 12	53 ± 6
Blood pressure >140/90 mm Hg	43	21	13	29
Diabetes mellitus (%)	29	0	13	14
Cigarette smoking (%)	43	64	50	86
Total cholesterol (mg/dl)	234 ± 29	224 ± 33	259 ± 36	250 ± 46
Angina class, CHA 3,4 (%)	29	72	87	71
Angina duration (mos)	5 ± 5	5 ± 6	9 ± 12	15 ± 11
Coronary artery narrowing (% diameter reduction)	63 ± 5	83 ± 9	91 ± 4	100 ± 0

CHA = Canadian Heart Association.

abling the determination of distal coronary occlusion pressure at the tip of the balloon. Pressures were determined with fluid-filled tubing and Statham P231D pressure transducers.

Acquisition of baseline data: A 5Fr pigtail catheter was advanced into the left ventricle and the angioplasty guiding catheter into the ascending aorta; left ventricular and aortic pressures were recorded. This was followed by baseline left ventriculography in the 30° right anterior oblique projection by injection of 40 ml of Renografin 38%. Subsequently, the pigtail catheter was removed and selective angiography of the contralateral coronary artery was performed by manual injection of 5 to 10 ml of Renografin-76.® Then, the guiding catheter was placed into the ostium of the vessel to be dilated and the lesion was visualized in several projections. Finally, the guidewire and angioplasty balloon were placed across the lesion and pressures at the tip of the balloon and in the aorta were recorded simultaneously.

Acquisition of intervention data: The lesion was dilated by 2 or 3 balloon inflations, sufficient to achieve prompt distal filling of the vessel around the deflated balloon. Following a rest period of 4 minutes, 3 additional balloon inflation cycles with a duration of 60 to 90 seconds each were performed during which data acquisition occurred. Three minutes of recovery were allowed between each of these inflations. Immediately before and during cycle 1, pressures were recorded continuously in the aorta, the left ventricle and at the tip of the balloon. During cycle 2, at 40 to 60 seconds of balloon inflation, a second left ventriculogram was acquired (Figures 1 and 2). During cycle 3, at 40 to 60 seconds, dye was injected manually into the contralateral coronary artery, to assess collateral status.

Data analysis: Lesion location and severity were assessed by a panel of 2 cardiologists who were not aware of any other patient findings. Lesions were grouped into 3 categories by location: right coronary artery, proximal left anterior descending artery and mid-left anterior descending artery.[18] The lesion and adjacent normal segment were traced using a magnified projection of the cineangiographic view demonstrating maximal severity. The diameters of the stenosed and adjacent normal segments were measured and lesion severity was expressed as percent reduction in lumen diameter.

Collateral classification: A panel of 2 cardiologists blinded to all other angiographic and clinical data qualitatively assessed collateral filling to the artery being dilated. Collateral filling of the obstructed vessel was classified based on presence and extent of epicardial filling by contralateral coronary artery injection at baseline and during balloon inflation, as follows: class 0 = no epicardial filling at baseline or during occlusion; class I = no epicardial filling at baseline with partial epicardial filling during balloon inflation; class II = partial epicardial filling at baseline with partial or complete filling during occlusion; class III = complete epicardial filling at baseline.

Pressures were measured at baseline and during balloon inflation in the first study cycle. The mean pressure measured at the tip of the angioplasty cathe-

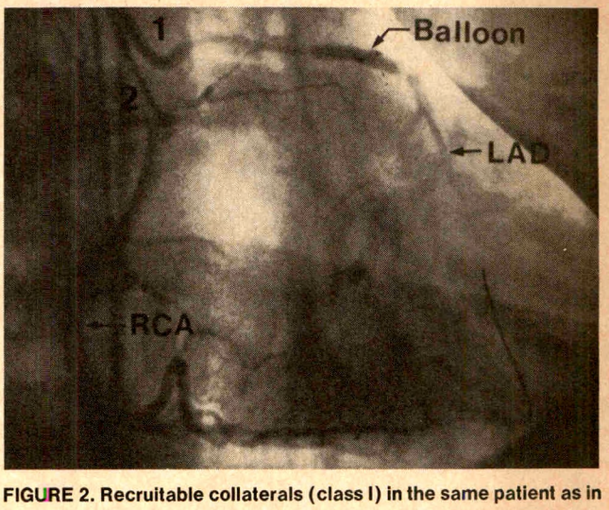

FIGURE 2. Recruitable collaterals (class I) in the same patient as in Figure 1. Dye injection into the right coronary artery (RCA) via catheter (*2*) during obstruction of the left anterior descending artery (LAD) by the inflated balloon results in filling of the mid-LAD beyond the site of occlusion via collateral channels. No collaterals were visible prior to ballon inflation. 1 = guiding catheter.

ter at 50 seconds of occlusion was called distal coronary occlusion pressure (DCOP). In the analysis of DCOP, a correction for mean aortic pressure was applied since these 2 pressures are related in a linear fashion and the majority of investigators assess the ratio DCOP/Pao.[16]

Left ventricular function: The left ventriculograms were acquired and analyzed with the Diasonics-Fischer digital subtraction imaging system. Calculation of ejection fraction was based on the area-length method.[19]

Statistics: The data went into an IBM XT computer. The SAS statistical software package was used to perform all statistical calculations. Comparisons among groups were made using chi-square tests for categorical variables and analysis of variance, and analysis of covariance for continuous variables. Differences in occlusion ejection fraction among collateral classes were assessed taking the 3 lesion location categories into consideration and adjusting for baseline ejection fraction. Linear regression methods were used to develop the model relating occlusion ejection fraction and DCOP/Pao.

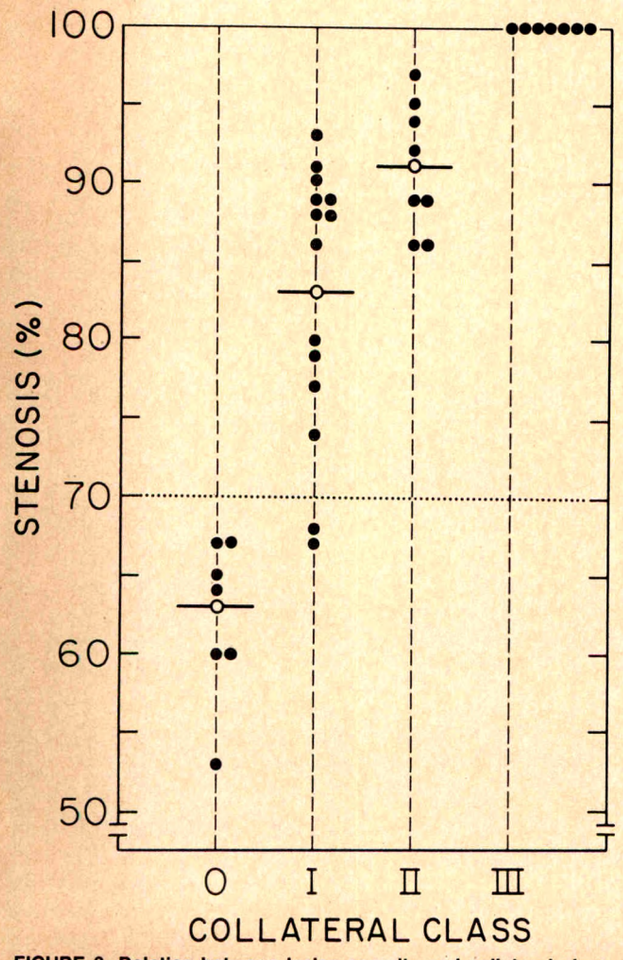

FIGURE 3. Relation between lesion severity and collateral class. ***Open circles*** **indicate mean values.**

Phase II. Clinical validation of the model: Based on the findings of phase I, the hypothesis was derived that the risk of hemodynamic collapse after abrupt coronary closure can be predicted by location and severity of the lesion prior to closure. Risk was predicted to be high with a proximal left anterior descending artery lesion <70%, intermediate with a proximal left anterior descending artery lesion >70%, low if there was a mid-left anterior descending artery or right coronary artery lesion. This hypothesis was tested in phase II in a second group of patients who experienced abrupt coronary closure as an angioplasty complication.

The study group included all 23 patients in a consecutive series of 1,300 procedures whose elective angioplasty of an isolated left anterior descending or right coronary artery lesion was complicated by total occlusion at the dilatation site. Preintervention lesion location and severity were assessed as in phase I of this study by investigators blinded to clinical outcome. The consequences of abrupt coronary occlusion were assessed in 2 categories: clinical outcome and treatment. Clinical outcome was defined by in-hospital vital status and immediate hemodynamic consequences of coronary artery occlusion. Treatment comprised the need for immediate interventions, such as intraaortic balloon counterpulsation due to severe ischemia with hemodynamic instability and emergency revascularization by either coronary artery bypass surgery or repeat angioplasty. Emergent bypass surgery was performed only in those patients who had ischemic pain persisting for more than 10 minutes after abrupt coronary closure.

Results

Phase I. Correlates of collateral indexes: The association between collateral class and 8 baseline vari-

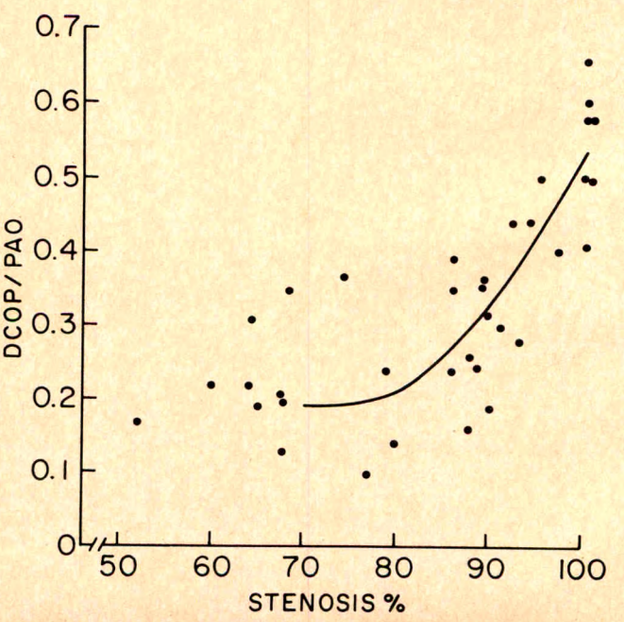

FIGURE 4. Relation between lesion severity and distal occlusion pressure/aortic pressure ratio (DCOP/Pao).

TABLE II Distal Coronary Occlusion Pressure/Aortic Pressure Ratio and Left Ventricular Ejection Fraction, Grouping the Patients by Collateral Class, Lesion Location and Severity

Lesion			Ejection Fraction (%)	
Location	Severity (%)	DCOP/Pao	Baseline	Occlusion
		Class 0		
PLAD	53	0.17	79	43
PLAD	64	0.22	86	29
PLAD	64	0.31	75	57
PLAD	67	0.20	72	31
MLAD	60	0.22	74	56
MLAD	65	0.19	74	55
MLAD	67	0.13	86	74
		Class I		
PLAD	68	0.35	80	67
PLAD	74	0.38	83	50
PLAD	79	0.24	82	56
PLAD	86	0.24	69	49
PLAD	89	0.36	63	45
PLAD	93	0.28	77	57
MLAD	67	0.21	70	63
MLAD	80	0.14	71	60
MLAD	89	0.36	73	66
MLAD	91	0.30	74	68
Right	77	0.10	75	65
Right	88	0.16	62	57
Right	88	0.26	76	64
Right	90	0.19	72	68
		Class II		
MLAD	86	0.35	80	59
MLAD	89	0.32	60	58
MLAD	95	0.50	75	74
Right	86	0.39	79	78
Right	89	0.24	85	79
Right	92	0.44	80	76
Right	94	0.44	75	70
Right	97	0.40	62	65
		Class III		
PLAD	100	0.58		
PLAD	100	0.59	38	
MLAD	100	0.41	70	
MLAD	100	0.66	62	
Right	100	0.60		
Right	100	0.50	72	
Right	100	0.50	61	

DCOP/Pao = distal coronary occlusion pressure/aortic pressure ratio; MLAD = mid-left anterior descending artery; PLAD = proximal left anterior descending artery; right = right coronary artery.

ables was assessed (Table I). Seven patients were classified as collateral class 0, 14 as class I, 8 as class II and 7 as class III. There was a significant difference between all 4 collateral classes in degree of lesion severity ($p < 0.05$) (Figure 3). Collateral class 0 was associated with a mean lesion severity of 63% (range 53 to 67%), class I with 83% (62 to 93%), class II with 91% (85 to 97%) and class III with 100% in all patients (Table I and II). The findings suggest that a lesion of >70% severity predicts the presence of angiographically demonstrable collaterals with a specificity of 100% and a sensitivity of 85% (Figure 3).

Patients of collateral class 0 had significantly less severe angina pectoris as assessed by Canadian Heart Association criteria than patients with angiographically demonstrable collaterals ($p = 0.02$). There was a trend toward an association between collateral class and duration of angina pectoris ($p = 0.13$).

With each increment in collateral class for either left or right coronary artery, the DCOP/Pao rose significantly (Tables II and III). The relation between DCOP/Pao and lesion severity was described by a quadratic equation: DCOP/Pao = $2.8809 - 0.0729 \times \text{stenosis} + 0.00049 \times \text{stenosis}^2$; $R^2 = 0.68$; $p = 0.0001$ (Figure 4).

Left ventricular ejection fraction: During balloon occlusion, the left ventricular ejection fraction was found to be significantly related to lesion location ($p < 0.01$) and both indexes of collateral flow ($p < 0.05$). When DCOP/Pao was considered, the regression equations for mid-left anterior descending artery and right coronary artery did not differ: occlusion ejection fraction = $59 + 26 \times$ (DCOP/Pao). For patients with proximal left anterior descending artery the equation was: occlusion ejection fraction = $24 + 89 \times$ (DCOP/Pao). The R^2 for the model was 0.59 (Figure 5).

When collateral class was considered, 4 significantly different groups were identified (Figure 6): (1) proximal left anterior descending/collateral class 0: mean occlusion ejection fraction = 39%; (2) proximal left anterior descending/collateral class I: occlusion ejection fraction = 54%; (3) mid-left anterior descending/

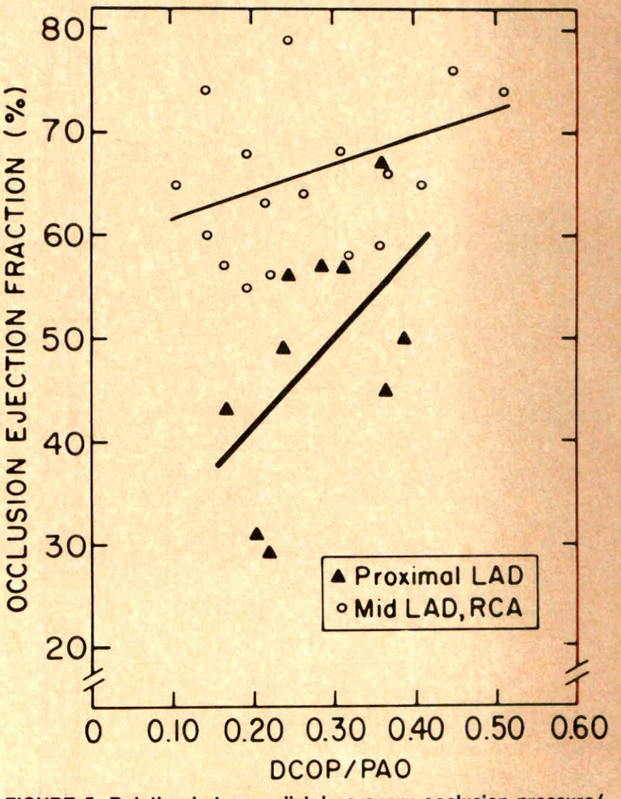

FIGURE 5. Relation between distal coronary occlusion pressure/aortic pressure ratio (DCOP/Pao), left ventricular ejection fraction during balloon inflation and lesion location. LAD = left anterior descending; RCA = right coronary artery.

collateral classes 0–II and right coronary artery/collateral classes 0–I: occlusion ejection fraction = 62%; (4) right coronary artery/collateral class II: occlusion ejection fraction = 73%. This was the only group in which the ejection fraction did not decrease during coronary closure.

Phase II: After abrupt coronary closure occurring as an angioplasty complication, both treatment and clinical outcome correlated with risk group assignment (Figure 7). The only deaths occurred in 2 of the 3 patients in the high-risk group. Cardiogenic shock occurred in all 3 patients of the high-risk group and in the 1 patient with the least severe lesion in the intermediate-risk group. Intraaortic balloon counterpulsation was used in 7 of 9 high- and intermediate-risk patients but in only 2 of the 14 low-risk patients. Emergency revascularization was performed in 8 of the 9 high- and intermediate-risk patients; 1 patient refused revascularization. Four of 14 low-risk patients did not evidence signs or symptoms of myocardial ischemia as a result of coronary obstruction and, therefore, did not undergo emergency revascularization.

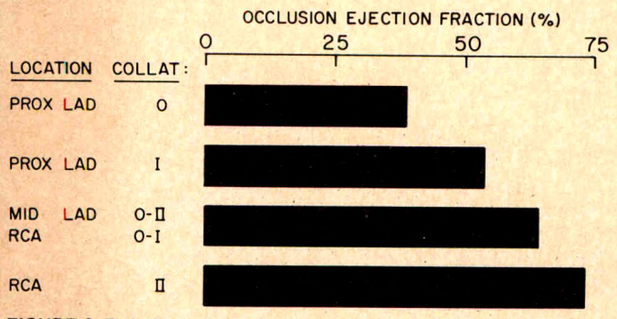

FIGURE 6. Relation between collateral class and mean left ventricular ejection fraction during balloon inflation in the proximal left anterior descending (PROX LAD), mid-left anterior descending (MID LAD) or right coronary artery (RCA).

RISK GROUP	Patient ID	Pre-stenosis (%)	TREATMENT		OUTCOME	
			Revasc	IABP	Shock	Death
HIGH	1	59	•	•	•	
	2	62			•	•
	3	67	•	•	•	•
INTERMEDIATE	4	73	X	•	•	
	5	90	•	•		
	6	92	X			
	7	94	•	•		
	8	95	•	•		
	9	96	•	•		
LOW	10	50		•		
	11	61	•			
	12	62	•			
	13	77	•			
	14	82	•			
	15	87	•			
	16	91	•			
	17	91				
	18	92	•	•		
	19	92	•			
	20	92	•			
	21	94	•			
	22	95				
	23	98				

FIGURE 7. Treatment and clinical outcome in 23 patients whose left anterior descending or right coronary artery angioplasty was complicated by abrupt coronary closure. Revasc = emergency revascularization by coronary bypass surgery (•) or repeat angioplasty (X). IABP = intraaortic balloon counterpulsation. For definition of risk groups refer to text.

Discussion

Threshold for collateral development: Although lesions with stenotic diameters ranging from 50 to 75% have occasionally been found in vessels receiving collateral flow,[20,21] lesion severity in collateralized vessels usually is at least 90% in most studies.[9,22] Our finding of a lesion severity of at least 86% in class II patients is in agreement with these reports. However, collaterals could be demonstrated during inflation of the angioplasty balloon in the majority of patients in whom they were not visible at baseline angiography. These collaterals, constituting class I in our classification, have been called "recruitable collaterals" in the literature.[13] The presence of such recruitable collaterals indicates that the frequency of collateral development in patients with coronary artery disease has been underestimated by standard angiographic techniques.

The existence of at least class I collaterals in all patients with a lesion having a diametric narrowing of >70% and the absence of any collateral filling during controlled coronary closure in almost all patients with <70% lesions suggest that this lesion severity may represent a threshold value for the development of collaterals in human hearts which are demonstrable by angiography during occlusion. The positive association between lesion severity and both indexes of collateral flow as assessed during coronary occlusion indicates that, beyond the threshold value, lesion severity and collateral development are quantitatively related. This relation probably applies only to patients with stable angina, such as those included in this study, who presumably have a chronic fixed coronary lesion.

Distal coronary occlusion pressure in humans and experimental animals: In dogs with chronic fixed constriction of the coronary artery, collateral flow was completely protective at the time of abrupt coronary ligation if the DCOP/Pao exceeded 0.5.[23] In the present study, we have demonstrated that patients with severe fixed coronary lesions may develop DCOP/Pao ratios comparable to those found in completely protected animals. This finding complements our previously published observation of complete preservation of local wall motion and absence of electrocardiographic signs of ischemia during balloon occlusion in patients with well-developed collaterals.[24]

Clinical importance of collateral flow: The findings of the present study suggest that the clinical conse-

quences of abrupt coronary closure result from an interaction between the location of the obstruction and the amount of collateral flow. The site of coronary obstruction determines the extent of myocardium at risk while the amount of collateral flow at the time of obstruction determines the degree of protection of that area.

In the case of right coronary artery or mid-left anterior descending obstruction, we observed DCOP/Pao values covering the entire spectrum of values reported in experimental studies. High DCOP/Pao values during occlusion in these patients were associated with complete or nearly complete preservation of global left ventricular function, indicating that the development of completely protective collaterals can be stimulated by a chronic subtotal lesion in humans. This hypothesis is supported by the lack of clinical signs of ischemia observed in some patients who experienced complete coronary occlusion of a high-grade lesion of the right coronary artery or the mid-left anterior descending branch as a complication of angioplasty in the second phase of this study. In those patients in whom the collateral indexes indicated minimal or absent collateral flow during right coronary artery or mid-left anterior descending balloon occlusion, the reduction of ejection fraction was moderate, reflecting the area of myocardium at risk. In the corresponding low-risk group of the second study phase, catastrophic events did not occur when percutaneous transluminal coronary angioplasty was complicated by coronary artery occlusion.

Collateral flow appears to be most important in patients with proximal left anterior descending occlusion, i.e., those patients who have a larger area at risk. Ejection fraction values during balloon occlusion were severely depressed in those patients in whom the collateral indexes indicated very low or absent collateral flow. Deaths occurred only in the corresponding high-risk group of the second study phase. Patients with recruitable collaterals had significantly higher ejection fraction values during proximal left anterior descending balloon inflation than those without collaterals. The corresponding intermediate-risk group of phase II was characterized by a more favorable clinical outcome than the high-risk group.

Limitations and conclusions: It is conceivable that the linear regression model shown in Figure 5 would not describe the relation between occlusion ejection fraction and DCOP/Pao accurately over a wider range of values. A leveling off toward a horizontal line at the high and low extremes of the spectrum would be expected.

It is possible that the nitrates and calcium antagonists uniformly applied during our studies affected collateral flow differently in the different collateral classes.[25-27]

Left ventricular function and collateral flow might not be the same 45 to 60 seconds after coronary closure and several hours thereafter.[11,28,29] The relation between left ventricular function immediately following coronary closure and clinical course over the subsequent hours is not known. In phase II of this study we have begun to address this problem by a retrospective analysis of clinical outcome in patients who experienced abrupt coronary closure as a complication of angioplasty. Conclusive testing of the model would require a prospective study of an analogous design.

In spite of their limitations, these models add to our understanding of the consequences of abrupt coronary closure in the natural history of symptomatic 1-vessel coronary artery disease. Clinical decisions are often based on the assumption that the prognostic importance of a lesion parallels its severity; however, the relation between lesion severity and collateral development shown with our model indicates an inverse relation between lesion severity and clinical consequences of abrupt coronary closure.

TABLE III Distal Coronary Pressure/Aortic Pressure by Collateral Class and Lesion Location

	Collateral Class			
Location	0	1	2	3
Right		18 (7)	38 (8)	56 (6)
LAD	21 (6)	29 (8)	39 (10)	56 (10)

Mean values (standard deviation).
LAD = left anterior descending artery; right = right coronary artery.

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Usefulness of Serial Radionuclide Monitoring During Graded Nitroglycerin Infusion for Unstable Angina Pectoris for Determining Left Ventricular Function and Individualized Therapeutic Dose

WARREN M. BREISBLATT, MD, NESTOR A. VITA, MD, MARCOS ARMUCHASTEGUI, MD, LAWRENCE S. COHEN, MD, and BARRY L. ZARET, MD

Using serial invasive hemodynamics in concert with noninvasive radionuclide monitoring of left ventricular (LV) function, 20 patients with unstable angina were evaluated during incremental infusion of intravenous nitroglycerin. Of 20 patients, 17 demonstrated a favorable hemodynamic response and dose responses could be determined for individual patients. There was excellent agreement between hemodynamic and noninvasive radionuclide measurements, and patient responses could be inferred from the radionuclide data alone. Cardiac output improved by 29% (mean 4.7 ± 1.2 to 6.0 ± 1.3), LV ejection fraction increased an average of 0.11 (0.39 ± 0.14 to 0.50 ± 0.16) and diastolic function as assessed by peak filling rate improved from 1.80 ± 0.60 end-diastolic volumes/s to 2.70 ± 0.90. Changes in systolic blood pressure and heart rate were not predictive of hemodynamic response. The dose of nitroglycerin necessary to produce maximal hemodynamic benefit was variable (mean 98 μg/min, range 48 to 144). In 7 patients, nitroglycerin caused excessive decreases in pulmonary arterial wedge pressure and adverse hemodynamics that corrected with intravenous fluids, allowing continued administration of intravenous nitroglycerin with improvement in hemodynamic status. In 15 patients, peak systolic pressure–end-systolic volume relations were assessed to define possible changes in LV contractility induced during nitroglycerin infusion. In 12 of these patients, this relation was linear, suggesting altered loading rather than augmented contractility as nitroglycerin's mechanism of action. In 3 patients a downward and rightward shift of the systolic relation was seen, suggesting that significant underloading with nitroglycerin was associated with depressed contractility.

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The use of intravenous nitroglycerin as a potential therapeutic modality in patients with coronary artery disease was first reported in 1962.[1,2] However, it is only relatively recently that intravenous nitroglycerin has been used widely in the treatment of patients with acute myocardial infarction and unstable angina.[3–6] Several studies have emphasized its therapeutic utility when added to conventional antianginal therapy in patients with unstable angina.[7–9] Nevertheless, questions remain concerning the optimal therapeutic dose of intravenous nitroglycerin in such patients, its effect (either positive or negative) on left ventricular (LV) performance in this circumstance and the optimal means of monitoring patients during therapy. The present study was undertaken to provide a framework within which to deal with these issues. Invasive hemodynamic measurement was both compared and used in concert with noninvasive serial radionuclide monitoring of LV function in a series of patients with unstable angina receiving incremental dose infusions of intravenous nitroglycerin. We attempted to: (1) compare

From the Cardiology Section, Yale University School of Medicine, New Haven, Connecticut. Manuscript received October 14, 1987; revised manuscript received December 24, 1987, and accepted December 26.

Address for reprints: Barry L. Zaret, MD, Yale University School of Medicine, Section of Cardiology, 333 Cedar Street, New Haven, Connecticut 06510.

TABLE I Hemodynamic Data

Pt		BP (mm Hg)	MAP (mm Hg)	PAWP (mm Hg)	CO (liters/min)	HR (bpm)	EF	PFR (EDV/s)	ESV (ml)	EDV (ml)	RSV	SV (ml)	IV NTG Dose (μg/min) at Peak Effect
1	B	156/88	111	21	4.1	82	0.51	3.06	61	109	0.60	48	100
	P	120/75	90	12	5.0	76	0.61	5.02	45	114	0.80	69	
2	B	115/80	92	26	6.6	102	0.20	2.02	252	319	0.22	67	78
	P	100/70	80	20	8.0	95	0.33	3.30	229	307	0.41	78	
3	B	125/80	95	28	4.5	56	0.45	2.55	92	167	0.70	75	130
	P	98/65	76	16	5.8	60	0.57	3.50	68	163	0.88	95	
4	B	108/70	83	19	4.4	68	0.18	1.31	152	217	0.19	65	48
	P	98/72	81	16	5.0	68	0.25	1.73	137	212	0.28	75	
5	B	130/90	103	28	4.3	76	0.16	0.50	155	213	0.17	58	84
	P	114/80	91	18	5.4	79	0.24	0.70	131	204	0.23	73	
6	B	100/60	73	23	3.3	75	0.20	0.80	180	225	0.21	45	96
	P	95/60	71	19	3.9	77	0.26	1.43	168	220	0.34	54	
7	B	110/80	90	24	5.2	75	0.24	1.57	118	188	0.25	70	84
	P	102/70	81	12	7.3	83	0.34	2.18	90	178	0.38	88	
8	B	108/82	91	12	5.3	67	0.39	1.68	128	207	0.30	79	72
	P	94/72	79	13	7.2	68	0.63	3.08	80	186	0.58	106	
9	B	130/75	93	14	3.6	58	0.49	1.90	69	129	0.62	60	108
	P	120/75	90	18	4.7	56	0.60	2.76	52	134	0.84	82	
10	B	118/72	87	26	4.2	66	0.58	2.24	55	117	0.42	62	96
	P	104/58	73	16	5.8	68	0.68	3.05	36	121	0.70	85	
11	B	118/90	99	26	3.4	55	0.54	1.74	70	132	0.48	62	60
	P	112/71	85	20	4.9	53	0.62	2.75	48	126	0.68	78	
12	B	110/72	85	2	4.4	56	0.52	1.63	60	135	0.71	75	144
	P	106/76	86	7	5.9	58	0.57	2.50	39	141	1.04	102	
13	B	120/90	100	4	7.3	110	0.39	2.22	43	109	0.51	66	72
	P	125/80	95	10	8.6	99	0.46	3.32	34	120	0.76	86	
14	B	102/80	87	2	3.5	62	0.43	2.10	98	155	0.48	57	132
	P	115/75	88	13	5.7	60	0.52	3.00	72	161	0.84	89	
15	B	160/80	106	14	6.6	66	0.51	2.28	96	196	0.58	100	108
	P	140/60	87	16	7.8	66	0.62	2.83	70	188	0.71	118	
16	B	120/78	92	18	4.7	72	0.48	1.37	79	143	0.40	64	84
	P	102/70	80	12	5.7	72	0.66	1.88	42	121	0.70	79	
17	B	120/76	91	10	4.8	75	0.49	1.67	68	131	0.48	63	96
	P	130/74	93	16	5.8	75	0.59	2.37	56	133	0.67	77	
18	B	115/80	92	10	5.2	100	0.17	1.40	98	150	0.20	52	120
	P	116/75	89	12	5.5	98	0.22	1.32	96	153	0.24	57	
19	B	100/70	80	12	4.5	82	0.52	2.63	70	125	0.51	55	120
	P	98/70	79	12	4.2	76	0.54	2.76	72	132	0.56	60	
20	B	120/65	83	16	4.2	65	0.48	2.58	68	132	0.66	64	108
	P	110/65	80	16	3.9	65	0.52	2.52	69	130	0.63	61	

B = baseline; BP = systemic blood pressure; bpm = beats/min; CO = cardiac output; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; HR = heart rate; IV NTG = intravenous nitroglycerin; P = peak therapeutic effect; PAWP = pulmonary arterial wedge pressure; PFR = peak filling rate; RSV = radionuclide stroke volume; SV = stroke volume.

the results of invasive and noninvasive monitoring in each patient and (2) assess the relation of changes in LV function to changes in contractility as inferred from evaluation of LV systolic pressure-volume relations.

Methods

Patient population: The study population consisted of 20 patients hospitalized with unstable angina pectoris: in 7 patients the unstable syndrome occurred in the peri-infarction period and in the remaining 13 patients there was either a marked change in a preexisting stable anginal pattern or the new onset of angina requiring hospitalization in a coronary care unit. All patients had been treated with 1 or more of the following: nonparenteral nitrate preparations (13 patients, 66%) β-blocking agents (14 patients, 70%), and calcium antagonist agents (9 patients, 45%) before initiation of intravenous nitroglycerin. Fourteen patients were receiving 2 or more antianginal agents before intravenous nitroglycerin. Patients ranged in age from 42 to 78 years (mean 59); 12 were men and 8 women. Eighteen of 20 patients were evaluated with coronary angiography. Eleven had 3-vessel disease, 4 had 2-vessel disease and 2 had 1-vessel disease (both involving high grade proximal left anterior descending coronary artery stenosis). Based on initial physical examination 6 patients were thought to have some manifestation of congestive heart failure.

Hemodynamic-radionuclide protocol: Nitroglycerin for parenteral use (400 μg/cc) was administered by infusion pump, starting at a dose of 10 μg/min. The dose was increased at 10 μg/min increments every 5 minutes. Patients were titrated to a maximal tolerated dose that was defined by either a 20% reduction in systolic blood pressure, a decrease in systolic blood pressure to a level of 90 mm Hg irrespective of the baseline value or development of intolerance to proto-

col duration or intolerable drug side effects. In 15 patients the study was performed at the bedside in the coronary care unit; in 5 it was obtained in the cardiac catheterization laboratory.

Before the institution of intravenous nitroglycerin all patients had a balloon-tip catheter placed in the pulmonary artery. In 14 patients blood pressure was monitored by arterial line. In the remaining 6 patients, a sphygmomanometer was used. Radionuclide monitoring of function was obtained with a nonimaging nuclear probe (Nuclear Stethoscope, Bios). Nuclear studies were obtained following equilibrium blood pool labeling with technetium-99m (25 mCi) according to a modified in vitro technique.[10] Standard probe positioning algorithms were used to define LV and background regions. Acquisition of individual electrocardiographic gated nuclear probe studies required 60 seconds. Radionuclide-determined parameters included LV ejection fraction, LV peak filling rate normalized to end-diastolic volume and radionuclide relative stroke volume. Background measurement was rechecked every 20 minutes. Hemodynamic measurements included heart rate, blood pressure, cardiac output, right atrial pressure, pulmonary artery pressure and pulmonary arterial wedge pressure. Cardiac output was determined in duplicate by thermodilution. LV volumes were derived from the relation between LV ejection fraction (by nuclear probe) and stroke volume (by thermodilution).

For each patient, hemodynamic and radionuclide data were obtained during the last minute at each dose level. In this manner individual dose-responses could be determined. Monitoring was continued when intravenous fluid therapy was administered because of the initial hemodynamic response to nitroglycerin.

In 15 patients LV peak systolic pressure-end systolic data were defined at each dose level of nitroglycerin. These points were plotted to define a systolic pressure-volume relation for each patient. Analysis of pressure-volume plots allowed assessment of changes in LV contractility possibly induced during nitroglycerin infusion.[11]

Statistical methods: Data are given as mean ± standard deviation. Linear correlations between parameters were derived in a standard manner. Differences between baseline and treatment effects within patient groups were assessed by paired *t* test.

Results

Hemodynamic responses: Intravenous nitroglycerin resulted in substantial improvement in hemodynamic status in the majority of patients studied (Table I). Within the confines of our protocol, 17 of 20 patients demonstrated a favorable hemodynamic response defined by an increase in cardiac output of at least 10%.[12] In these 17 patients, cardiac output improved by 29% (range 14 to 55). Mean baseline cardiac output increased from 4.7 ± 1.2 to 6.0 ± 1.3 liters/min ($p < 0.004$) at the time of maximal augmentation. Heart rate remained unchanged (72 ± 16 at baseline versus 71 ± 18 beats/min at the time of peak effect). Systolic blood pressure decreased by 11 ± 12 mm Hg at the time of maximal hemodynamic effect. Baseline systolic blood pressure averaged 121 ± 16 mm Hg and was 110 ± 13 at the time of peak effect. Peak hemodynamic improvement occurred over a wide range of wedge pressures in individual patients. The nitroglycerin dose necessary to produce maximal hemodynamic benefit within the protocol constraints likewise was quite variable. The mean dose at the time of maximal improvement in cardiac output was 98 μg/min (range 48 to 144).

Radionuclide parameters demonstrated comparable levels of improvement in the 17 responders. LV ejection fraction improved, with an average increase of 0.11 ± 0.05. This increase is far in excess of the

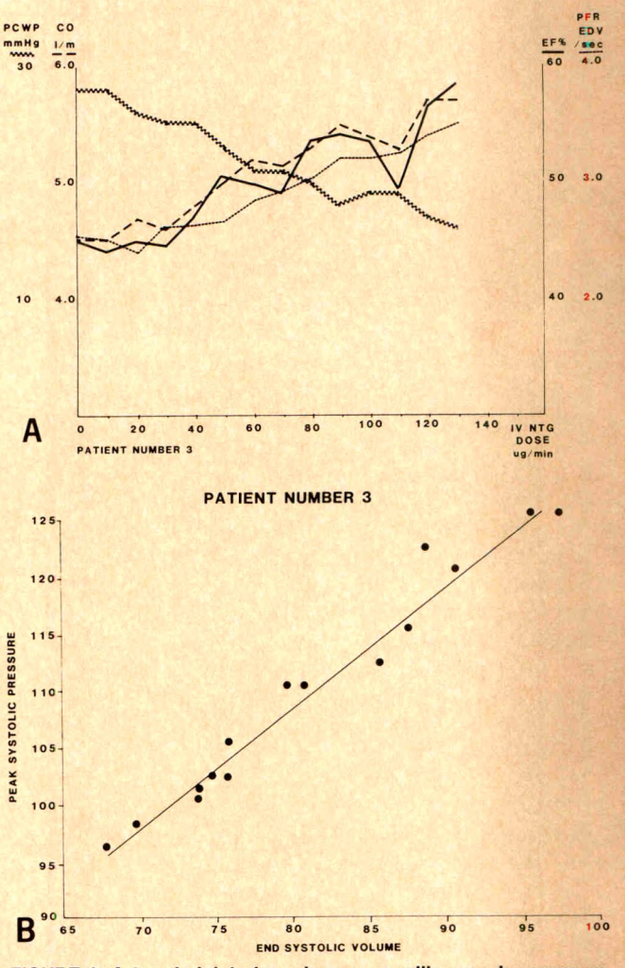

FIGURE 1. *A*, trended data for pulmonary capillary wedge pressure (PCWP), cardiac output (CO), ejection fraction (EF) and peak filling rate (PFR) during the incremental dose infusion of intravenous nitroglycerin (IV NTG). Data were obtained at each dose. The dose of IV NTG is plotted on the horizontal axis and the hemodynamic parameters on the vertical axis. Note that with the incremental dose of nitroglycerin there is a progressive increase in EF (*solid lines*) and PFR, associated with an increase in CO and a decrease in PCWP. *B*, the peak systolic pressure–end-systolic volume plot in the same patient is shown. Note that this relation remains linear, indicating that the changes encountered are related to altered loading conditions.

TABLE II Correlation Coefficients of Radionuclide and Hemodynamic Parameters

Pt	CO-EF	SV-RSV	PFR-EF
1	0.92	0.95	0.80
2	0.81	0.81	0.98
3	0.97	0.99	0.95
4	0.65	0.75	0.95
5	0.74	0.92	0.82
6	0.66	0.86	0.86
7	0.91	0.88	0.70
8	0.95	0.96	0.92
9	0.84	0.96	0.92
10	0.98	0.98	0.92
11	0.96	0.84	0.86
12	0.83	0.96	0.88
13	0.87	0.86	0.84
14	0.90	0.96	0.92
15	0.89	0.98	0.88
16	0.94	0.99	0.96
17	0.90	0.91	0.94
18	0.87	0.72	0.84
19	0.60	0.94	0.82
20	0.88	0.86	0.90

SV = stroke volume (measured by thermodilution); other abbreviations as in Table I.

intrinsic variability of the measurement.[13,14] Mean baseline LV ejection fraction was 0.39 ± 0.14 and this increased to 0.50 ± 0.16 at the time of maximal hemodynamic effect ($p < 0.05$). The individual range of improvement was 0.05 to 0.24. Relative radionuclide stroke volume increased from 0.43 ± 0.18 to 0.64 ± 0.23 (52%). End-diastolic volume did not change significantly: 165 ± 52 cc at baseline and 162 ± 48 at time of peak effect, whereas end-systolic volume decreased from 105 ± 43 to 80 ± 13 cc ($p < 0.05$). LV diastolic function, as assessed by peak filling rate also improved, increasing from 1.80 ± 0.60 to 2.70 ± 0.90 end-diastolic volumes/s at peak dose ($p < 0.004$). Changes in filling rate correlated closely with changes in LV ejection fraction in individual patients (Table II). The r value averaged 0.87 and ranged from 0.70 to 0.98 in individual patients.

Favorable responses also were seen in the 10 patients in whom filling pressures were elevated (wedge pressure ≥18 mm Hg). In these patients wedge pressure decreased from 24 ± 4 to 16 ± 3 mm Hg at peak effect. In these same patients systolic blood pressure decreased from 120 ± 34 to 104 ± 7 mm Hg. As in the group as a whole, there was no change in heart rate in these patients (73 vs 73 beats/min). In this subgroup cardiac output increased from 4.4 ± 0.9 to 5.7 ± 1.2 liters/min and LV ejection fraction increased from 0.35 ± 0.17 to 0.46 ± 0.19. There were no significant differences between responses to nitroglycerin in patients with significant elevation in wedge pressure and those 10 patients without such elevation. Improvement in LV ejection fraction and cardiac output also were similar. However, those patients with lower LV filling pressure often needed an elevated wedge pressure, achieved through fluid administration, to obtain maximal hemodynamic effect. Neither changes in blood pressure nor heart rate predicted hemodynamic responses. Comparable trends were also seen in the 7 patients with peri-infarction angina.

Comparison of serial radionuclide and hemodynamic data: In general, there was excellent agreement between hemodynamic and radionuclide measurements in this protocol (Table II). The correlation between thermodilution cardiac output and LV ejection fraction in each patient averaged r = 0.85. In 16 of 20 patients, r was >0.80. Thermodilution stroke volume correlated well with radionuclide relative stroke volume, with r averaging 0.90. The r value was 0.80 in 18 of 20 patients. The parallel nature of the responses of invasive and noninvasive parameters is illustrated in Figures 1 and 2.

Use of intravenous fluids with nitroglycerin: In 7 patients (patients 7 through 11, 15, 17) nitroglycerin

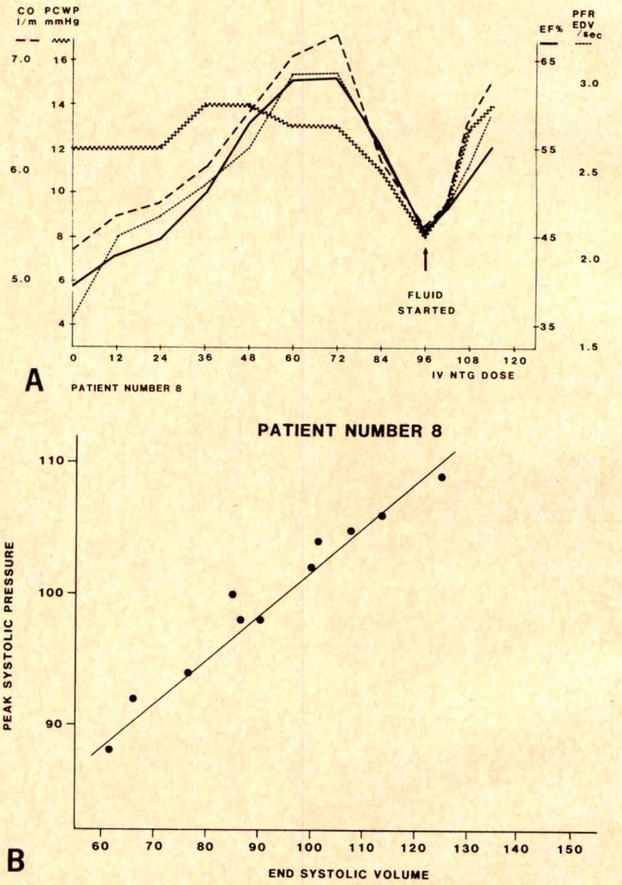

FIGURE 2. *A*, relation between cardiac output (CO), pulmonary capillary wedge pressure (PCWP), ejection fraction (EF) and peak filling rate (PFR) during an incremental nitroglycerin infusion in a patient requiring intravenous volume to maintain effective forward output. The format is the same as in Figure 1. Note the tracking of the radionuclide and invasive parameters as well as the substantial improvement achieved after fluid infusion. *B*, the peak systolic pressure–end-systolic volume plot in the same patient is shown. Despite significant increments and decrements in ejection fraction, this pressure-volume relation remains linear. One can infer from this that no change in contractility has occurred.

TABLE III The Role of Volume Expansion During Intravenous Therapy*

	Systolic BP (mm Hg)	HR (bpm)	EF	PCWP (mm Hg)	PFR	CO (liters/min)	RSV
Baseline	114	66	0.44	22	1.87	4.5	0.45
Peak (initial)	105	68	0.56	16	2.72	6.3	0.65
Trough	95	69	0.47	11	2.05	5.1	0.53
After intravenous fluids	107	68	0.54	17	2.56	6.1	0.62

* Data from 7 patients (7 through 11,15,17) receiving a mean of 340 cc intravenous fluids (range 200 to 500). Abbreviations as in Table I.

caused excessive decreases in wedge pressure associated with decreases in systemic blood pressure and symptoms, but no appreciable change in heart rate (Table III). In these patients, intravenous fluids were used to increase filling pressures and allow continued administration of intravenous nitroglycerin (Figure 2 and Table III). In these patients, 200 to 500 cc of intravenous fluid (normal saline) was administered (mean 340). With the falling pressure there was a decrease in cardiac output, blood pressure, ejection fraction, filling rate and relative stroke volume. Hemodynamic status was reversed with fluids and there was good tracking between invasive and noninvasive measures.

Systolic pressure-volume relations: Linear peak systolic pressure–end-systolic volume relations were demonstrated in each of the 15 patients so evaluated. An average of 10 pressure-volume points were obtained for each patient. The correlation coefficient for the 15 patients averaged 0.87 (range 0.56 to 0.98). In 11 of 15 patients r was >0.80. The linearity of the relation suggests that although LV ejection fraction was increasing during therapy, this was the result of altered loading rather than augmented contractility. As noted previously, when nitroglycerin resulted in excessive decreases in filling pressures, there was an associated decrease in cardiac output and LV ejection fraction. In most instances the decrease in ejection fraction occurred with no alteration in the linear nature of the systolic pressure-volume relation. However, in 3 patients (Figure 3) this was accompanied by a shift of the systolic pressure-volume relation downward and to the right. In 2 of these 3 patients there was either associated recurrent chest pain or ST-segment alteration. In these 3 patients, we postulate that underloading after intravenous nitroglycerin resulted in a sufficient decrease in coronary perfusion pressure to result in ischemia-related altered left ventricular contractility. It should be emphasized that this was seen in relatively few patients.

Discussion

Use of intravenous nitroglycerin is an important aspect of contemporary care. This therapy has been applied to patients with acute myocardial infarction, congestive heart failure and acute hypertension after cardiac surgery. Perhaps its most important application lies in the management of patients with unstable angina. Although this therapy currently is employed widely, there still is no general agreement concerning definition of both optimal therapy and objective monitoring criteria. The present study demonstrates that under carefully monitored conditions, substantial hemodynamic improvement can be demonstrated in most patients receiving graded nitroglycerin infusion. Although serial observation with pulmonary artery catheters still remains the appropriate current standard for therapeutic monitoring, this study also illustrates the potential of serial noninvasive monitoring. The measured noninvasive parameters both complement as well as correlate with invasively derived data.

Within the confines of our protocol, maximal improvement in hemodynamic status as judged by cardiac output was not predicated by achieving either a single dose of nitroglycerin or a specific decrement in systolic blood pressure. A decrease in mean systemic blood pressure of 10% has been advocated as a means of effectively and safely titrating intravenous nitroglycerin.[12] Only 35% of patients in our series would have noted a maximal hemodynamic effect if such a

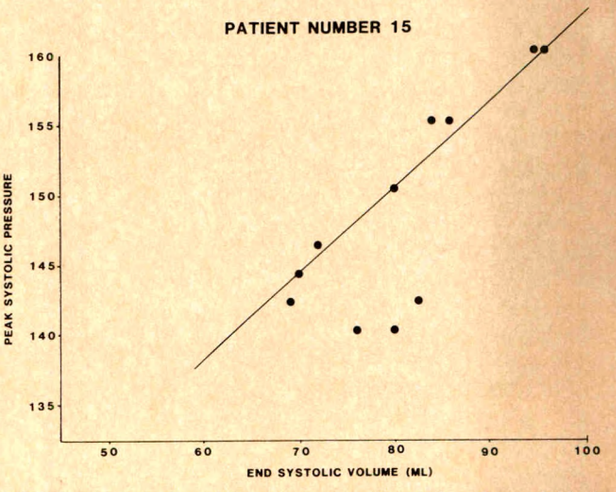

FIGURE 3. The peak systolic pressure–end-systolic volume plot in 1 of 3 patients requiring intravenous volume during intravenous nitroglycerin and also manifesting an abnormal systolic pressure-volume relation. In contrast to the previous example, in this patient there are several points in the systolic pressure-volume relation that are below and to the right of the linear relation. This suggests decreased contractility, presumably due to coronary underperfusion associated with a marked decrease in filling pressures and forward output due to intravenous nitroglycerin.

protocol had been followed. On the other hand, it is clear that a protocol of continuing graded increments in nitroglycerin dose can result in deleterious hemodynamic effects, with substantial reduction in filling pressures and subsequent decrease in cardiac output and LV performance. For these reasons, detailed but nevertheless simple monitoring of hemodynamic status should be considered. In this series, noninvasive parameters tracked and paralleled hemodynamic data quite well, thereby suggesting a possible future role in monitoring therapy. Significant correlations between invasive and noninvasive data were obtained in each patient. The concept of noninvasive monitoring for optimization of therapy clearly merits further prospective evaluation.

Radionuclide monitoring was obtained with a nonimaging nuclear probe. This instrument is relatively compact when compared with conventional scintillation cameras.[13,14] However, when considered as a means of serial monitoring of the acutely ill patient, its size and positioning pose potential logistic problems. These problems conceivably can be solved with miniaturized detector apparatus that can either be affixed directly on the chest wall or worn by the patient.[15-18]

From a mechanistic standpoint, changes in LV function were generally related to altered loading circumstances. This was inferred from observation of the systolic pressure-volume relations. Nevertheless, in a small subset of patients actual changes in contractility did occur. Although in this study ventricular volumes were measured by combining ejection fraction and thermodilution stroke volume measurements, actual ventricular volume measurements can be obtained with radionuclide data when appropriate attenuation correction is used. The use of systolic pressure-volume relations to differentiate changes in loading from those due to altered contractility clearly is an important issue that can be addressed directly by this approach. The use of peripheral systolic pressure to obtain an estimate of peak systolic pressure is well accepted.[19]

It was somewhat surprising that in our patients, despite a decrease in end-systolic volume, end-diastolic volume did not decrease. This suggests that under these circumstances, the effects of intravenous nitroglycerin were more evident on the resistance than capacitance circulation. The concomitant administration of other vasoactive drugs may have contributed to this somewhat paradoxical event. Changes in diastolic performance, as measured by peak filling rate, paralleled closely those in LV ejection fraction. This suggests that nitroglycerin effects on diastolic function were not necessarily independent, but rather linked, at least in part, to changes in systolic performance.

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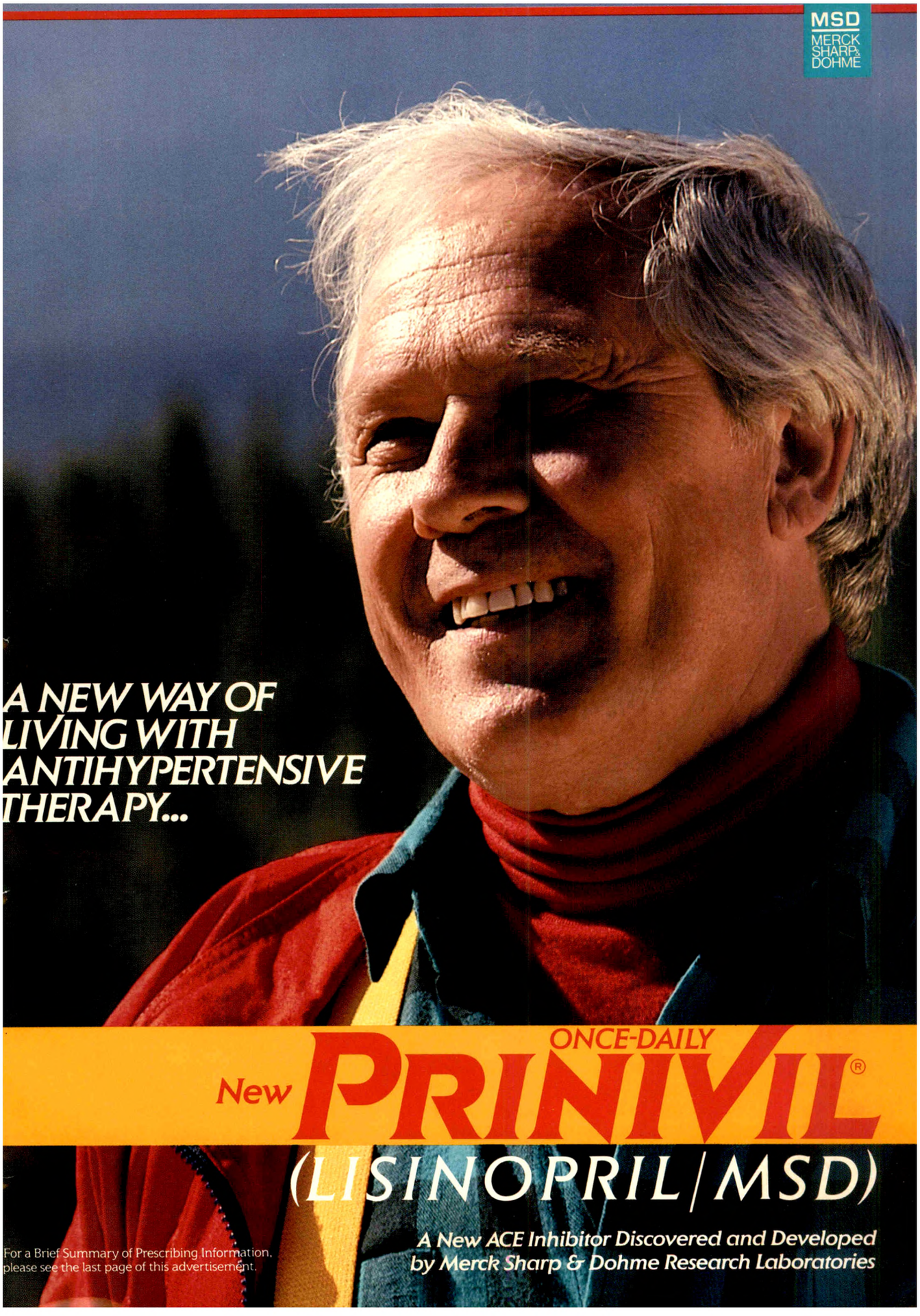
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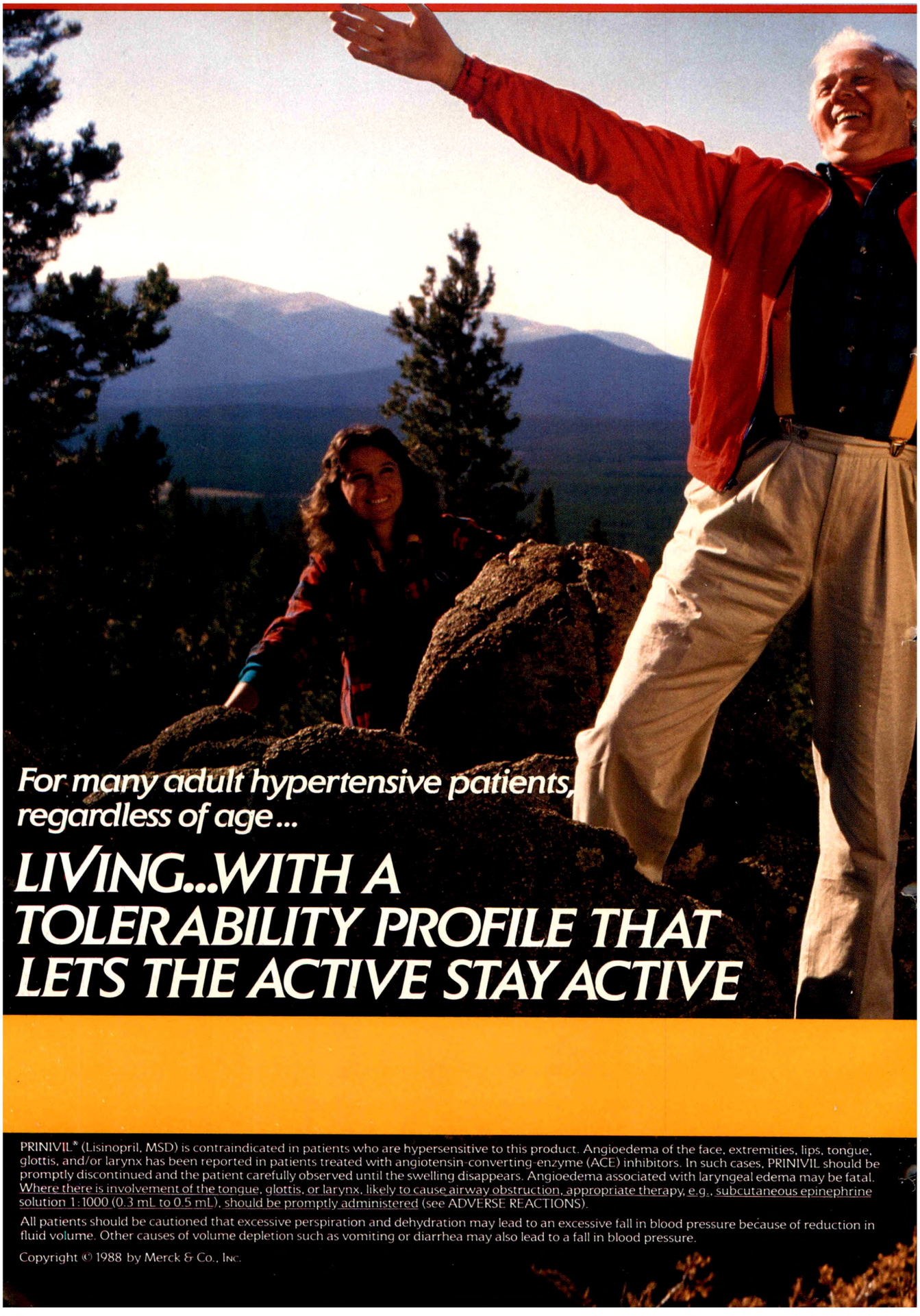

PRINIVIL® (Lisinopril, MSD) is contraindicated in patients who are hypersensitive to this product. Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with angiotensin-converting enzyme (ACE) inhibitors. In such cases, PRINIVIL should be promptly discontinued and the patient carefully observed until the swelling disappears. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered (see ADVERSE REACTIONS).

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure.

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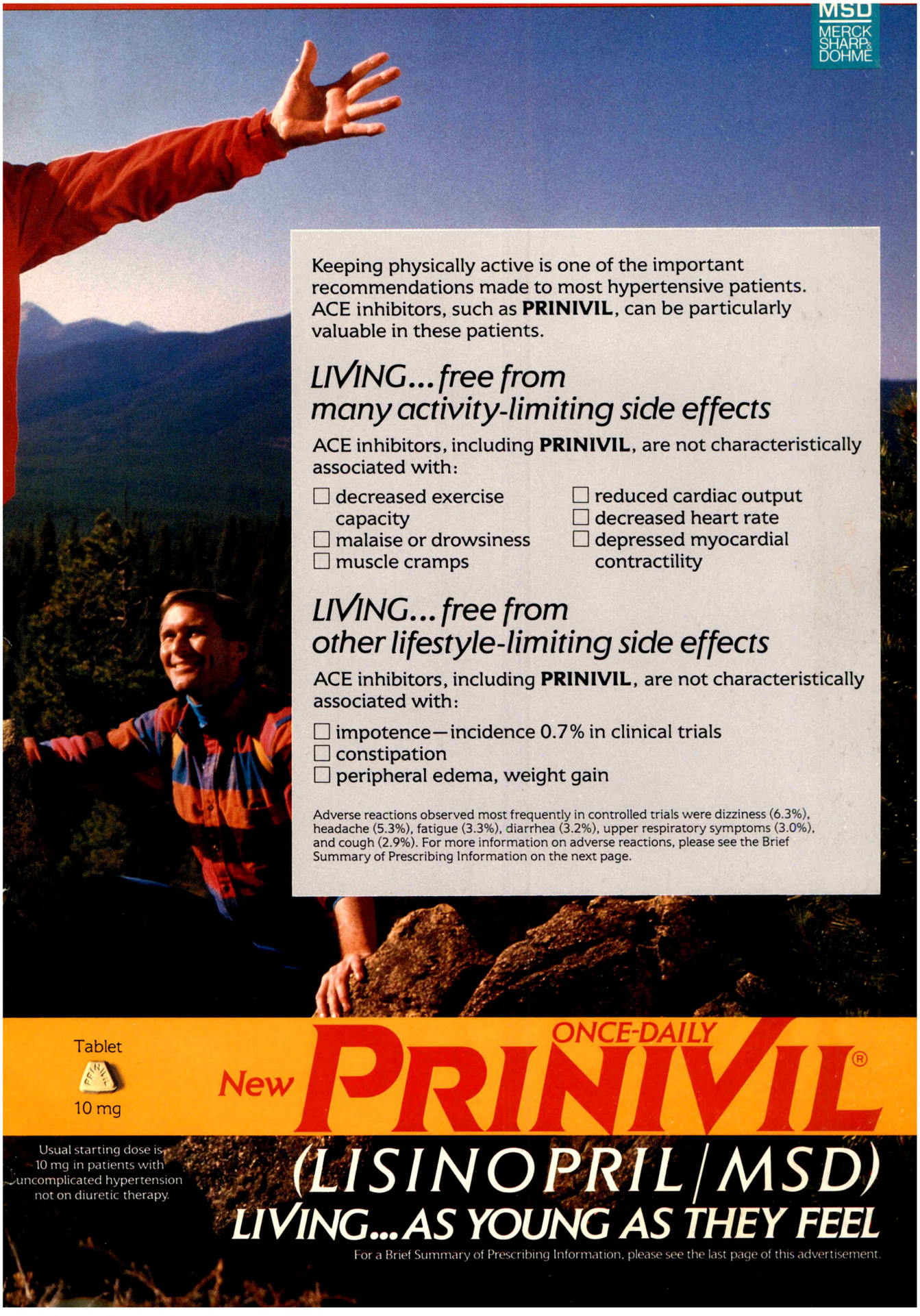
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LIVING... free from other lifestyle-limiting side effects
ACE inhibitors, including **PRINIVIL**, are not characteristically associated with:
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☐ peripheral edema, weight gain
Adverse reactions observed most frequently in controlled trials were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%). For more information on adverse reactions, please see the Brief Summary of Prescribing Information on the next page.
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Warnings:
Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including PRINIVIL. In such cases, PRINIVIL should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered** (see ADVERSE REACTIONS).
Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of the use of PRINIVIL in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis (see PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first 2 weeks of treatment and whenever the dose of PRINIVIL and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.
If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.
Neutropenia/Agranulocytosis: Another ACE inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of PRINIVIL are insufficient to show that PRINIVIL does not cause agranulocytosis at similar rates. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions:
General: Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including PRINIVIL, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.
In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another ACE inhibitor suggests that these increases are usually reversible upon discontinuation of PRINIVIL and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy.
Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when PRINIVIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of PRINIVIL and/or discontinuation of the diuretic may be required.
Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).
Hyperkalemia: In clinical trials, hyperkalemia (serum potassium > 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases, these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with PRINIVIL (see *Drug Interactions*).
Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, PRINIVIL may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.
Information for Patients:
Angioedema: Angioedema, including laryngeal edema, may occur, especially following the first dose of PRINIVIL. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.
Symptomatic Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, patients should be told to discontinue the drug until they have consulted with the prescribing physician.
All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician.
Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.
Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.
NOTE: As with many other drugs, certain advice to patients being treated with PRINIVIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.
Drug Interactions:
Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with PRINIVIL® (Lisinopril, MSD). The possibility of hypotensive effects with PRINIVIL can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with PRINIVIL. If it is necessary to continue the diuretic, initiate therapy with PRINIVIL at a dose of 5 mg daily, and provide medical supervision after the initial dose for at least 2 hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS and DOSAGE AND ADMINISTRATION). When a diuretic is added to the therapy of a patient receiving PRINIVIL, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic (see DOSAGE AND ADMINISTRATION).
Indomethacin: In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of PRINIVIL alone were compared to PRINIVIL given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant.
Other Agents: PRINIVIL has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when PRINIVIL was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of PRINIVIL.
Agents Increasing Serum Potassium: PRINIVIL attenuates potassium loss caused by thiazide-type diuretics. Use of PRINIVIL with potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.
Pregnancy Category C: Lisinopril was not teratogenic in mice treated on days 6 to 15 of gestation with up to 1,000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1,000 mg/kg, this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6 to 17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2 to 7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation.
Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline-supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to ACE inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man. Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at a dose of lisinopril at 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day).
There are no adequate and well-controlled studies in pregnant women. PRINIVIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when PRINIVIL is given to a nursing mother.
Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions:
PRINIVIL has been found to be generally well tolerated in controlled clinical trials involving 2,003 patients and subjects.
The most frequent clinical adverse experiences in controlled trials with monotherapy with PRINIVIL were: dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range.
Other adverse experiences occurring in greater than 1% of patients and subjects treated with monotherapy with PRINIVIL in controlled clinical trials were: nausea (2.3%), hypotension (1.8%), rash (1.5%), orthostatic effects (1.4%), asthenia (1.3%), chest pain (1.3%), vomiting (1.3%), and dyspnea (1.1%). For information on adverse experiences occurring in greater than 1% of patients and subjects treated with PRINIVIL plus hydrochlorothiazide in controlled clinical trials, see Prescribing Information.
Clinical adverse experiences occurring in 0.3% to 1% of patients treated with monotherapy with PRINIVIL in the controlled trials and rarer, serious, possibly drug-related events reported in uncontrolled studies or marketing experience included: *Body as a Whole:* Chest discomfort, fever, flushing. *Cardiovascular:* Angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, palpitation. *Digestive:* Abdominal pain, anorexia, constipation, flatulence. *Metabolism:* Gout. *Musculoskeletal:* Joint pain, shoulder pain. *Nervous System/Psychiatric:* Depression, somnolence, insomnia, stroke. *Respiratory System:* Bronchitis, sinusitis, pharyngeal pain. *Urogenital:* Oliguria, progressive azotemia, acute renal failure. *Other:* Blurred vision, pruritus, urinary tract infection, vasculitis of the legs. *Angioedema:* Angioedema has been reported in patients receiving PRINIVIL® (Lisinopril, MSD) (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with PRINIVIL should be discontinued and appropriate therapy instituted immediately (see WARNINGS). *Hypotension:* In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.5% of hypertensive patients (see WARNINGS). In patients with congestive heart failure, hypotension occurred in 5% and syncope occurred in 1% of patients. These adverse experiences were cause for discontinuation of therapy in 1.3% of these patients.
Clinical Laboratory Test Findings:
Serum Electrolytes: Hyperkalemia (see PRECAUTIONS).
Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2% of patients with essential hypertension treated with PRINIVIL alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis (see PRECAUTIONS). Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased.
Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g % and 1.3 vol %, respectively) occurred frequently in patients treated with PRINIVIL but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.
Other (Causal Relationship Unknown): Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.
Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%), and serum potassium (0.4%).

Dosage and Administration:
Initial Therapy: In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20 to 40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give a greater effect. If blood pressure is not controlled with PRINIVIL alone, a low dose of a diuretic may be added. Hydrochlorothiazide 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of PRINIVIL.
Diuretic-Treated Patients: In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of PRINIVIL. The diuretic should be discontinued, if possible, for 2 to 3 days before beginning therapy with PRINIVIL to reduce the likelihood of hypotension (see WARNINGS). The dosage of PRINIVIL should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with PRINIVIL alone, diuretic therapy may be resumed as described above.
If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least 2 hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS and PRECAUTIONS, *Drug Interactions*).
Concomitant administration of PRINIVIL with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).
Use in Elderly: In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of PRINIVIL. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution.
Dosage Adjustment in Renal Impairment: The usual dose of PRINIVIL (10 mg) is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≥ 10 mL/min and ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis), the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486. *J8PV09(501)*

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Acute Effects of Felodipine in Exertional Angina Pectoris

SABINO SCARDI, MD, CLAUDIO PANDULLO, MD, FULVIO PIVOTTI, MD, GIULIANO CESCHIA, MD, and GIORGIO POLLAVINI, MD

To investigate the antianginal efficacy, duration of action and tolerability of 2 doses of the new calcium antagonist felodipine, 15 patients (14 men and 1 woman, mean age 62 years) with stable exertional angina pectoris and angiographically demonstrated coronary artery disease were randomly given felodipine, 5 and 10 mg, and placebo on 3 different days. A bicycle ergometer exercise test was performed 3 and 10 hours after dosing. In comparison with placebo, felodipine 5 and 10 mg significantly increased resting heart rate and decreased resting systolic and diastolic blood pressure 3 hours after administration ($p < 0.001$). Ten hours after administration, only supine systolic blood pressure was still significantly lower ($p < 0.001$). Anginal (time to mild chest pain) and ischemic (time to 1 mm ST depression) thresholds, as well as duration of exercise and total work at peak exercise, were higher in comparison with placebo at 3 and 10 hours ($p < 0.001$). In comparison with the lower dose, 10 mg felodipine induced a decrease in supine ($p < 0.05$) and sitting ($p < 0.01$) systolic blood pressure at rest and an increase in total work to anginal threshold ($p < 0.01$), as well as in total work and duration of exercise at peak exercise ($p < 0.05$). These results suggest that a single administration of felodipine, 5 and 10 mg, may improve exercise capacity over a 10-hour period in patients with stable exercise-induced angina due to atherosclerotic heart disease.

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Felodipine, a recently developed dihydropyridine derivative, is a calcium antagonist that selectively reduces smooth muscle contractile activity, particularly in resistance vessels.[1,2] Reduction in peripheral vascular resistance and, consequently, in arterial blood pressure account for the decrease in left ventricular systolic pressure, which is one of the 2 major determinants of cardiac afterload. The drug does not seem to have any effect on preload[1]: left ventricular end-diastolic pressure, revealed by pulmonary arterial wedge pressure measurements, remains unchanged after the oral administration of 0.1 mg/kg of felodipine to patients with coronary artery disease and exertional angina pectoris.[3] Hemodynamic effects of felodipine on coronary blood flow have also been demonstrated.[4] Coronary vasodilatation and, therefore, an increase in myocardial oxygen supply have been documented during cardiac catheterization as shown by an increase in coronary sinus flow, an increase in oxygen saturation of coronary sinus blood and a decrease in myocardial arteriovenous oxygen difference.[3,5] The present study evaluates the antianginal efficacy, duration of action and tolerability of 2 doses of felodipine (5 and 10 mg) after acute oral administration in patients with chronic, stable, exercise-induced angina pectoris.

Methods

Patient selection: Outpatients with a history of exercise-induced angina pectoris that was stable over a period of at least 6 months, and in whom angina was relieved by rest and sublingual nitroglycerin, were considered for the study. Patients had to have angiographic evidence of coronary artery disease. However, only those patients who had previously performed an exercise test, which was stopped because of typical chest pain associated with ST-segment depression ≥1 mm, were included in the study.

Exclusion criteria: Exclusion criteria included exertional angina pectoris with variable threshold, mixed angina and angina at rest, evidence of coronary spasm during angiography, acute myocardial infarction during the previous 6 months, heart failure, congenital or valvular heart disease, cardiomyopathy, Lown class 3 to 4 ventricular arrhythmias, atrioventricular or intraventricular conduction disturbances, left

From the Centro Cardiovascolare, Ospedale Maggiore, Trieste, Italy. Manuscript received September 23, 1987; revised manuscript received December 3, 1987, and accepted December 4.

Address for reprints: Sabino Scardi, MD, Centro Cardiovascolare, Ospedale Maggiore, 34129 Trieste, Italy.

TABLE I Resting Heart Rate (HR) and Blood Pressure (BP), 3 and 10 Hours After Placebo and Felodipine, 5 and 10 mg

Variable	Position	Hours After Dosing	Placebo (1)	Felodipine 5 mg (2)	Felodipine 10 mg (3)	Analysis of Variance p	Orthogonal Comparisons (2) (3) vs (1) p	Orthogonal Comparisons (2) vs (3) p
HR (beats/min)	Supine	3	65 ± 8	72 ± 10	76 ± 10	<0.001	<0.001	NS
		10	69 ± 11	71 ± 11	72 ± 11	NS	—	—
	Sitting	3	76 ± 11	86 ± 11	89 ± 12	<0.001	<0.001	NS
		10	80 ± 8	82 ± 11	82 ± 13	NS	—	—
SBP (mm Hg)	Supine	3	159 ± 16	141 ± 14	132 ± 16	<0.001	<0.001	<0.05
		10	168 ± 19	150 ± 16	147 ± 18	<0.001	<0.001	NS
	Sitting	3	145 ± 19	132 ± 15	123 ± 17	<0.001	<0.001	<0.01
		10	147 ± 15	146 ± 16	142 ± 19	NS	—	—
DBP (mm Hg)	Supine	3	85 ± 8	79 ± 9	75 ± 10	<0.003	<0.004	NS
		10	86 ± 10	84 ± 8	84 ± 10	NS	—	—
	Sitting	3	81 ± 10	77 ± 9	71 ± 10	<0.001	<0.001	<0.05
		10	83 ± 14	84 ± 10	81 ± 12	NS	—	—

Data are mean ± standard deviation.
D = diastolic; NS = difference not significant; S = systolic.

TABLE II Heart Rate, Systolic Blood Pressure and Pressure-Rate Product at Ischemic (ST-Segment Depression = 1 mm) Threshold and at Peak Exercise

Variable	Hours After Dosing	Placebo (1)	Felodipine 5 mg (2)	Felodipine 10 mg (3)	Analysis of Variance p	Orthogonal Comparisons (2) (3) vs (1) p	Orthogonal Comparisons (2) vs (3) p
Ischemic threshold							
HR (beats/min)	3	107 ± 16	123 ± 17	125 ± 15	<0.001	<0.001	NS
	10	107 ± 12	119 ± 22	120 ± 27	NS	—	—
SBP (mm Hg)	3	180 ± 21	182 ± 24	179 ± 19	NS	—	—
	10	179 ± 21	175 ± 30	179 ± 21	NS	—	—
Pressure-rate product (10^{-2})	3	195 ± 44	226 ± 49	218 ± 38	<0.003	<0.003	NS
	10	193 ± 37	206 ± 44	213 ± 48	NS	—	—
Peak exercise							
HR (beats/min)	3	122 ± 17	137 ± 14	137 ± 13	<0.001	<0.001	NS
	10	123 ± 15	134 ± 22	135 ± 24	NS	—	—
SBP (mm Hg)	3	192 ± 25	196 ± 20	187 ± 22	NS	—	—
	10	197 ± 26	188 ± 30	195 ± 22	NS	—	—
Pressure-rate product (10^{-2})	3	235 ± 49	267 ± 31	257 ± 37	<0.01	<0.01	NS
	10	243 ± 47	249 ± 45	262 ± 40	NS	—	—

Data are mean ± standard deviation.
Abbreviations as in Table I.

ventricular hypertrophy, previous myocardial infarction of the anterior wall, Wolff-Parkinson-White syndrome, use of digitalis, antiarrhythmic, anticoagulant or psychotropic drugs and any abnormalities in the electrocardiogram at rest that might mislead the interpretation of ST-segment changes. Patients older than 70 years or with insulin-dependent diabetes, anemia (red cell count <3,000,000/ml) and serious hepatic or renal disease were also excluded.

Study design: The trial plan consisted of an acute, double-blind, within-patient, randomized study comparing felodipine, 5 and 10 mg, and placebo, each given once, according to a 3 × 3 latin square design, and replicated 5 times. Blindness was preserved by means of the double-dummy technique. After informed consent was obtained, previous antianginal therapy was withdrawn (1 week for β blockers, 3 days for nitrates and calcium antagonists). During the study, sublingual nitroglycerin was allowed to interrupt, but not to prevent, anginal attacks.

One week before entering the study, the patients performed 2 exercise tests on 2 consecutive days (at the same time of day) to verify reproducibility. The tests were considered reproducible (and the patient admitted to the study) if ischemic (time to 1 mm ST-segment depression) and anginal (time to mild chest pain) thresholds did not vary by >15%. During these sessions, the patients were instructed on how to recognize anginal pain and to classify it according to the method of Borg,[6] and were made familiar with the instruments and the laboratory staff. Eligible patients were then randomly given the 3 treatments in 3 different sessions, with a 24-hour interval between them. Study medications (placebo or felodipine 5 or 10 mg, orally)

TABLE III Heart Rate, Systolic Blood Pressure and Pressure-Rate Product Under the Same Load (Exercise Stopped with Placebo)

Variable	Hours After Dosing	Placebo (1)	Felodipine 5 mg (2)	Felodipine 10 mg (3)	Analysis of Variance p	Orthogonal Comparisons (2) (3) vs (1) p	Orthogonal Comparisons (2) vs (3) p
HR (beats/min)	3	112 ± 14	117 ± 15	117 ± 13	NS	—	—
	10	116 ± 10	117 ± 12	117 ± 11	NS	—	—
SBP (mm Hg)	3	182 ± 24	177 ± 19	170 ± 19	NS	—	—
	10	192 ± 28	187 ± 19	183 ± 17	NS	—	—
Pressure-rate product (10^{-2})	3	205 ± 44	206 ± 38	201 ± 38	NS	—	—
	10	224 ± 44	219 ± 36	215 ± 33	NS	—	—

Data are mean ± standard deviation.
Abbreviations as in Table I.

were administered at 7 A.M. and exercise testing was performed at 10 A.M. and 5 P.M., 3 and 10 hours after administration, respectively.

Exercise testing: Exercise testing was always performed on the same electromagnetically braked bicycle ergometer, following the protocol of Redwood et al.[7] The initial workload was 30 watts below the mean maximal workload reached during the 2 preliminary tests, with increases of 30 watts every 3 minutes. Systolic and diastolic blood pressure (cuff sphygmomanometer), heart rate and electrocardiogram recordings were taken at rest (supine and sitting) before the test. The same recordings were made every minute during exercise and the recovery phase, which lasted until all the parameters returned to baseline. Three electrocardiogram leads (V_2, V_5, and aVF) were also continuously monitored during the entire test. The test was stopped if typical chest pain of mild intensity (Borg class 4 to 5), horizontal or downsloping ST depression ≥3 mm and lasting at least 0.08 seconds from the J point, fatigue or physical exhaustion occurred. ST-segment depression and heart rate were monitored and calculated by a computer-assisted system (CASE II, Marquette Electronics Inc.). The study was carried out in accordance with the Declaration of Helsinki.

Evaluation of results: Results were evaluated on the basis of variations in heart rate, systolic and diastolic blood pressure and pressure-rate product measured at rest, at ischemic threshold (1 mm ST depression), at maximal workload reached during placebo and at peak exercise. Duration of exercise and total work were considered at the onset of pain (anginal threshold), at ischemic threshold and at peak exercise.

Statistical analysis: One-way analysis of variance and nonparametric tests were performed to check the homogeneity of patient distribution in the 3 sequences of treatment. Analysis of variance for latin square design was used to compare the 3 treatments. Orthogonal comparisons were performed when appropriate.

Patients: Fifteen outpatients, selected from a population of 53, were admitted to the study, and none was withdrawn after randomization. There were 14 men and 1 woman. Mean age was 62 years (range 55 to 70). Angina had been stable over a period ranging from 6 to 10 months, with an average of 3.1 weekly attacks. Ten patients had had a previous myocardial infarction. Coronary angiography showed 1-vessel disease in 1 patient, 2-vessel in 10 and 3-vessel in 4 patients.

Results

As the analysis of variance did not show either period or sequence effects, results are given according to the drug, irrespective of the sequence of treatment.

Effect on hemodynamic parameters at rest: As shown in Table I, felodipine both 5 mg and 10 mg induced a significant increase in heart rate and a decrease in systolic and diastolic blood pressure, 3 hours after administration ($p < 0.001$) in both supine and sitting positions compared with placebo. Systolic blood pressure in the supine position was still significantly lower after 10 hours ($p < 0.001$). As far as comparisons between the 2 dosages were concerned, the 10 mg dose significantly decreased supine systolic blood pressure and systolic and diastolic blood pressure in sitting position at 3 hours. No significant differences were found at 10 hours after administration.

Effects on hemodynamic parameters during exercise: Three hours after administration, both doses of felodipine induced a significant increase in heart rate and pressure-rate product at the anginal and the ischemic thresholds and at peak exercise. There were no differences between doses. No significant differences were found after 10 hours (Table II). Furthermore, during felodipine treatment, heart rate, systolic blood pressure and pressure-rate product, measured at the same workload reached during placebo, did not change significantly (Table III).

Effects on exercise capacity: Changes in exercise capacity, 3 and 10 hours after dosing, are listed in Table IV. In comparison with placebo, both doses of felodipine induced a highly significant improvement in duration of exercise and in total work ($p < 0.001$) at 3 and 10 hours after administration. No significant differences were found between the 2 doses. A significant increase in the duration of exercise to the onset of angina as well as in total work was observed, at both 3 and 10 hours. At 10 hours, the amount of work was significantly higher with felodipine 10 mg than with the 5 mg dose ($p < 0.01$). In comparison with placebo, duration of exercise and total work significantly in-

TABLE IV Duration of Exercise and Total Work Performed at Ischemic (ST-Segment Depression = 1 mm) and Anginal (Mild Severity) Thresholds and at Peak Exercise

Variable	Hours After Dosing	Placebo (1)	Felodipine 5 mg (2)	Felodipine 10 mg (3)	Analysis of Variance p	Orthogonal Comparisons (2) (3) vs (1) p	Orthogonal Comparisons (2) vs (3) p
Ischemic threshold	3	220 ± 77	327 ± 99	330 ± 99	<0.001	<0.001	NS
(s)	10	166 ± 74	229 ± 97	255 ± 88	<0.001	<0.001	NS
Anginal threshold	3	305 ± 80	440 ± 91	418 ± 79	<0.001	<0.001	NS
(s)	10	261 ± 87	338 ± 92	361 ± 114	<0.001	<0.001	NS
Duration of exercise	3	375 ± 89	479 ± 83	470 ± 76	<0.001	<0.001	NS
to peak exercise (s)	10	303 ± 86	367 ± 89	418 ± 109	<0.001	<0.001	<0.05
Total work to ST↓	3	1,193 ± 674	1,927 ± 1,042	2,004 ± 1,131	<0.001	<0.001	NS
1 mm (Kpm)	10	797 ± 530	1,189 ± 835	1,407 ± 943	<0.001	<0.001	NS
Total work to angina	3	1,655 ± 685	3,108 ± 1,340	2,743 ± 960	<0.001	<0.001	NS
(Kpm)	10	1,436 ± 777	1,911 ± 854	2,305 ± 1,071	<0.001	<0.001	<0.01
Total work to peak	3	2,366 ± 1,102	3,533 ± 1,286	3,277 ± 955	<0.001	<0.001	NS
exercise (Kpm)	10	1,718 ± 794	2,288 ± 830	2,716 ± 1,024	<0.001	<0.001	<0.05

Data are mean ± standard deviation.

creased 3 and 10 hours after administration, with both felodipine 5 mg and 10 mg. A significant difference ($p < 0.05$) was also found between the 2 doses at 10 hours.

During placebo, the test was always stopped because of angina associated with ST depression ≥3 mm. In contrast, during felodipine therapy (both doses), the test was stopped because of physical exhaustion, in 3 patients at 3 hours and in 1 patient at 10 hours. In the remaining patients, the reasons for stopping the test were angina associated with ST depression ≥1 mm or angina or ST depression ≥3 mm alone.

Adverse effects: One patient taking placebo, 3 patients taking felodipine 5 mg and 1 taking felodipine 10 mg experienced mild headache. One patient complained of asthenia and 1 of skin rash; both were taking felodipine 10 mg. None of the reported side effects caused the patients to withdraw. PR and QRS intervals, measured by electrocardiographic tracings, remained unchanged.

Discussion

The net effect of calcium antagonists on the cardiovascular system is the result of a complex set of interactions. Previous investigations have demonstrated that felodipine has a pronounced arteriolar vasodilator activity,[2,4] which results in an increase in cardiac output, stroke volume and coronary blood flow. This type of response has been described in patients with hypertension and coronary artery disease, with either normal or abnormal left ventricular wall motion.[8,9] In patients with congestive heart failure, the drug increases cardiac index, stroke volume and coronary flow without increasing myocardial oxygen consumption.[10]

Only preliminary data concerning the antianginal efficacy of felodipine are available. It has been shown that felodipine improves coronary blood flow. In particular, Emanuelson et al[11] reported an increase in luminal diameter of 7% in that portion of a coronary artery proximal to a stenosis, of 9% at the site of the stenosis and of 7% in the poststenotic portion after the intravenous administration of felodipine. Detry et al[12] examined the hemodynamic and antianginal effects of 0.1 mg/kg of felodipine after oral administration in patients with exercise-induced angina pectoris. At rest and during submaximal exercise, felodipine increased heart rate and decreased systemic blood pressure and vascular resistance. In comparison with baseline values, the patients showed an improvement in exercise capacity (20%), which was associated with a decrease in mean pulmonary wedge pressure and an increase in maximal cardiac output (20%), whereas the pressure-rate product remained unchanged. Recently Sheridan et al,[13] comparing the effects of felodipine with those of placebo in patients with stable angina pectoris treated with β-adrenoceptor blockers, showed that, at a plasma concentration of 15.5 nmol liter^{-1}, felodipine significantly increases exercise duration but fails to attenuate the degree of ST-segment depression during exercise.

The hemodynamic changes induced by felodipine, observed in our study, are similar to those reported by other investigators. Our data also indicate that felodipine has a favorable effect on exercise capacity. In comparison with placebo, exercise duration and total work at the appearance of angina, at the onset of 1 mm ST depression and at peak exercise were significantly higher with felodipine, both 3 and 10 hours after administration. The improvement in exercise capacity was associated with a significant increase in heart rate and pressure-rate product at peak exercise, suggesting a felodipine-related improvement in coronary blood flow. The absence of angina and of ST changes in patients given felodipine, at the workload reached with placebo, gives further support to this hypothesis. No significant differences between the 2 dosages were found at 3 hours after administration. However, 10 mg seemed to have a more prolonged duration of action than 5 mg; we observed a longer lasting improvement in duration of exercise and in total work at peak exercise ($p < 0.05$), as well as in total work until the onset of angina ($p < 0.01$). These findings are supported by the pharmacokinetic data obtained by Hedner et al,[14] who

showed that the mean elimination half-life of felodipine 10 mg, in steady-state conditions, is 23 ± 11 hours.

Clinical implications: The results of the present study show that felodipine, 5 and 10 mg, significantly increase exercise tolerance and prolong the ischemic and anginal thresholds up to 10 hours after oral administration in patients with chronic, stable, exercise-induced angina pectoris. At 3 hours after administration, the 2 doses are equally effective, but the 10 mg dose seems to produce more prolonged effects. Moreover, the drug is well tolerated. These properties indicate a useful role for felodipine in the management of outpatients with exertional angina pectoris. Further investigations are needed to determine its efficacy in long-term treatment.

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Correlation of Minimum Coronary Lumen Diameter with Left Ventricular Functional Impairment Induced by Atrial Pacing

JONATHAN TOBIS, MD, DAVID SATO, MD, ORHAN NALCIOGLU, PhD, WARREN D. JOHNSTON, MD, JOHN MALLERY, MD, JACKIE SEE, MD, LIAN QU, MS, TIM REESE, BS, JIM PAYNTER, RCPT, STEVE MONTELLI, CRT, and WALTER L. HENRY, MD

To understand whether quantitative measurement of minimal coronary luminal diameter is a better method than percent diameter narrowing for assessing the functional impairment of myocardial contractility produced by coronary artery stenoses, measurements were made from 37 stenotic segments in 27 patients with coronary artery disease and from corresponding segments in 10 subjects without coronary artery narrowing. An assessment of the reliability of the 2 types of measurements was made by correlating them with the physiologic parameters of both segmental wall motion and global ejection fraction response induced by atrial pacing. Digitally acquired coronary angiograms were used to facilitate quantitative analysis. Measurements by edge detection and videodensitometry correlated closely ($r = 0.94$). Percent diameter narrowing correlated moderately with the change in ejection fraction ($r = -0.41$) or with the change in segmental wall motion ($r = -0.44$). The measurement of minimal lumen diameter correlated with the change in global ejection fraction ($r = 0.61$) and did so even better with the change in segmental wall motion ($r = 0.78$, $p < 0.05$). A minimal lumen diameter of ≤ 1.5 mm identified patients likely to have a functional impairment during atrial pacing as assessed by either global ejection fraction or segmental wall motion defects. We conclude that minimal coronary luminal diameter provides a better method than percent diameter narrowing calculations to measure the anatomic severity of coronary artery narrowing.

(Am J Cardiol 1988;61:697–703)

The severity of coronary artery disease (CAD) is usually graded from angiograms by the percent narrowing between the stenotic segment and a more proximal normal portion.[1,2] Therefore, percent diameter narrowing is a relative number that depends both on the size of the narrowed as well as the presumed normal segments. One problem with this method of measurement is that identification of the presumed normal region is arbitrary. In addition, pathologic studies indicate that atherosclerosis is present to a variable degree in a large portion of so-called normal segments.[3] An alternative method of performing quantitative analysis of coronary angiograms is to measure the minimal lumen diameter instead of the percent diameter narrowing at the region of maximal arterial narrowing.[4] Theoretically, this minimal lumen diameter would be a more accurate way of comparing studies or interpreting the results of coronary angioplasty. However, there have been no clinical studies demonstrating that measurements of minimal lumen diameter correlate better than percent diameter narrowing with functional determinations of the severity of disease. The purpose of this study was to assess the correlation of both percent diameter narrowing and minimal lumen diameter with functional measurements of global ejection fraction and segmental wall motion during ischemia induced by atrial pacing.

From the Division of Cardiology and Department of Radiological Sciences, University of California, Irvine, California. This study was supported in part by grant RO1 HL31440-01A1 from the National Institutes of Health, Bethesda, Maryland. Manuscript received September 9, 1987; revised manuscript received and accepted December 4, 1987.

Address for reprints: Jonathan Tobis, MD, Division of Cardiology, UCI Medical Center, 101 City Drive South, Orange, California 92668.

Methods

Angiographic technique: Coronary angiograms were obtained by on-line digital acquisition. Images were exposed on a 7-inch image intensifier at a nominal focal spot of 1.2 mm. The images were converted by an on-line video image processor (Fischer DA-100)

into a 512 × 512 × 8 bit matrix and stored digitally on a 475 megabyte rapid parallel transfer disk (Fujitsu). Selective coronary angiograms were obtained in orthogonal right and left anterior oblique projections with cranial and caudal angulation. A more detailed description of our digital coronary acquisition and validation method as compared with 35-mm film cineangiography has been reported.[5]

Cardiac catheterization was performed by retrograde cannulation from the femoral artery and coronary angiograms were obtained and reviewed. A baseline digital subtraction left ventriculogram was then performed.[6,7] If there were no contraindications, an atrial pacing study was carried out. Contraindications to atrial pacing included significant left main disease, unstable angina, recent myocardial infarction (<3 months), cardiomyopathy or valvular heart disease. Left ventriculograms were performed in the 30° right anterior oblique projection to identify wall motion abnormalities in the distribution of the left anterior descending and right coronary arteries. To compare results of global ejection fraction and segmental wall motion in the right anterior oblique projection, no patients were included with predominant lesions in the circumflex artery (which would require left ventriculograms in the left anterior oblique projection to visualize lateral wall motion abnormalities).

Pacing protocol: After the resting digital left ventriculogram was obtained, 6Fr pacemaker electrode was inserted into the femoral vein and passed under fluoroscopic control to the lateral wall of the right atrium. The right atrium was stimulated at 2 mA initially at a rate of 10 beats/min above the patient's heart rate at rest. The rate was increased in increments of 10 beats/min every minute until chest pain developed or until a heart rate of 150 beats/min was reached. If atrioventricular Wenckebach block developed, 1 mg of atropine was administered intravenously and the pacing study continued. When the endpoint was achieved, another digital left ventriculogram was performed and the pacemaker was then turned off.

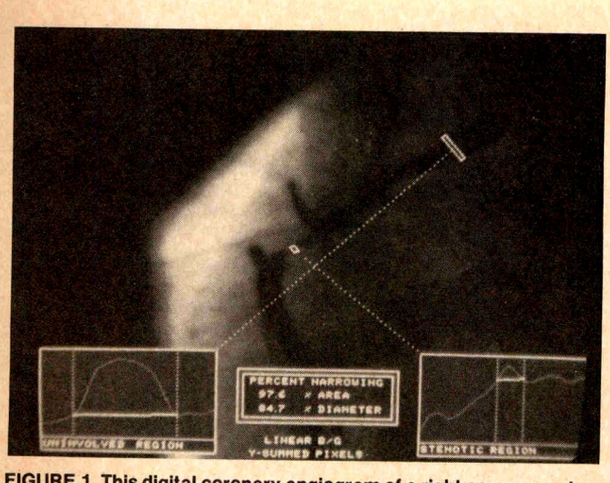

FIGURE 1. This digital coronary angiogram of a right coronary artery demonstrates a severe obstruction in the middle segment. Two regions of interest are defined at the obstruction and at a more proximal (assumed normal) segment. Because the image is already in a computerized format, the density of contrast within the lumen is calculated and plotted with the Y axis representiing relative density and the X axis corresponding to a 50-pixel wide segment perpendicular to the long axis of the artery. The densitometric boundary of the artery is then chosen and the percent area stenosis is calculated.

Quantitative analysis: After the catheterization was completed, the coronary angiographic images were recalled from computer memory. An individual frame was chosen from either the right anterior oblique or left anterior oblique projection which most clearly demonstrated the stenotic segment. Studies were chosen for analysis if the stenosis involved the proximal half of the right coronary artery or the left anterior descending coronary artery. This digital image was in an unsubtracted format, all calculations of the severity of coronary artery narrowing being made from the unsubtracted image so that measurement errors due to misregistration would not be introduced. The observer chose the stenotic portion of the image and the computer digitally magnified the area of interest 4-fold. Two different methods of quantifying the stenosis were used. The first was an edge-detection method with the operator choosing the diameter boundaries of the presumed normal and stenotic arterial segments. The image was magnified so that the catheter was displayed on the monitor screen and the edges of the catheter were defined by the operator. The routine angiographic catheters had been measured by Vernier calipers and these known measurements were used to calibrate the pixel dimensions of the digital image. Because the image was already in a digital X-Y coordinate matrix, the measurements of relative percent stenosis as well as absolute lumen dimensions could be quickly derived.

The second method of measurement of the stenosis was by videodensitometry (Figure 1). Because the unsubtracted digital images were logarithmically amplified to correct for exponential x-ray absorption, the digital number in each pixel corresponded to the thickness of the contrast material that the x-rays traversed. The observer chose the normal and stenotic segments by placing a rectangular region of interest over portions of the coronary image. The underlying background densities not due to contrast media in the arterial lumen were subtracted out by a linear averaging method, with the densities at the 4 corners of the region of interest used to estimate the underlying background.[8] In order to assure that a reasonable background measurement was obtained, the computer displayed the density profile of the arterial segment across the width of the artery. The observer could then alter the width of the region of interest so that it was just beyond the densitometric edge of the image as determined by the sharp inflection of the density profile. After subtracting out background densities, the density within each region of interest corresponded to the volume of contrast within the lumen. When divided by the height of the region of interest, this number corresponds to the cross-sectional area. The ratio of the densities at the stenotic and presumed normal segments was used to compute the percent area stenosis.

In order to compare videodensitometric results with the edge detection method, the percent diameter narrowing was derived from the percent area stenosis by assuming a circular cross section for the 2 segments. The minimum lumen diameter was then derived by using the width of the catheter to calibrate the distances in the image. The measurements of all the stenoses were performed by 2 independent observers. The first observer identified the regions of the artery to be measured and recorded their location with Polaroid® film so that both observers would derive measurements from approximately the same segments.

The digital left ventriculograms were analyzed by standard area-length methods for calculating volumes and ejection fraction.[9] The images were recalled from computer memory and processed by mask mode subtraction using a 10 to 15 frame blurred mask to enhance contrast.[10] The operator outlined the boundary of the end-diastolic and end-systolic images using the cursor of the computer graphics system. A separate wall motion analysis was performed on the ventricular boundaries using the method developed by Alderman et al.[11] In this analysis, the perimeter of the left ventricle in the right anterior oblique projection was divided into 5 segments (anterobasal, anterior, apical, diaphragmatic and posterobasal). The wall motion in these segments along radians was calculated and a percent of area segmental motion derived.

The relative amount of radial area shortening can be compared to a graph of wall motion based on normal subjects. For the purpose of this study, the percent of segmental area shortening was calculated at rest and during atrial pacing. The value at rest was subtracted from the value during pacing so that an increase in contractility during pacing would appear as a positive number and a decrease in contractility as a negative number. Similarly, the change in global ejection fraction was calculated as the value at rest subtracted from the value during pacing; thus, a fall in ejection fraction during pacing would appear as a negative value.

Statistical analysis: The measurements of percent diameter narrowing by the edge detection and videodensitometric techniques were compared by a linear regression analysis. The measurements of percent diameter narrowing and minimal lumen diameter were correlated to the change in global ejection fraction as well as to the change in segmental wall motion by separate linear regression analyses. Volumetric parameters at rest were compared with the values during pacing by a paired *t* test. Differences between groups of patients were compared with an unpaired *t* test.

Results

There were 41 patients who underwent atrial pacing studies. Four of these studies were excluded because either the resting or pacing left ventriculogram was not sufficiently opacified or it had multiple premature ventricular contractions which could have affected the wall motion analysis. There were 10 patients with chest pain syndromes who were found to have normal coronary angiograms and had atrial pacing studies performed. In the 27 patients with coronary artery narrowing, 22 were men and 5 women. The mean age was 54 ± 10 years. There were 35 narrowed coronary segments measured. There were 19 patients with 1-vessel disease and 8 with narrowed segments in both the left anterior descending and right coronary arteries; however, the second stenosis measured <50% and was judged not to be significant angiographically. Patients with complete occlusions or those with evidence of collateral blood supply were excluded. Of the 27 primary stenoses analyzed, 18 were in the left anterior descending, 8 in the right coronary artery and 1 was in a large diagonal artery. In the 27 patients with stenoses, the atrial pacing study induced chest pain in 15 (56%) and positive electrocardiographic criteria for ischemia was induced in only 8 (35%).

TABLE I Patients with Coronary Artery Disease

Clinical Variables	Rest (n = 27)	Atrial Pacing (n = 27)
Heart rate (beats/min)	69 ± 9	137 ± 13*
End-diastolic volume (ml)	153 ± 43	103 ± 33*
End-systolic volume (ml)	59 ± 37	51 ± 36†
Stroke volume (ml)	90 ± 30	52 ± 20*
Ejection fraction (%)	64 ± 15	54 ± 20*
Segmental wall radial shortening (%)	60 ± 22	48 ± 28†

* $p < 0.001$; † $p < 0.02$.

The mean percent diameter narrowing of the 27 primary lesions was 60 ± 16% when measured by the edge detection technique and it was not significantly different when measured by videodensitometry (60 ± 18%). The minimal lumen diameter was calculated to be 1.4 ± 0.6 mm by the edge detection method and 1.4 ± 0.7 mm by the densitometric technique (p = not significant). There was a close correlation (r = 0.94) between measurements of individual stenoses by edge detection and videodensitometry over the 0.4 to 2.8 mm range. In addition, interobserver variability was very close with either edge detection (r = 0.90) or videodensitometric technique (r = 0.89). There was no difference in the mean measurement of minimal lumen diameter for the left anterior descending artery obstructions (1.2 ± 0.4 mm) versus the right coronary artery obstructions (1.6 ± 0.6 mm).

The mean age of the 10 patients without CAD was 53.6 years (range 36 to 65), which was not different than the mean age of the patients with CAD. The mean ejection fraction at rest was 66 ± 7% and increased to 72 ± 5% at peak pacing ($p < 0.001$). The results of the ventricular volumetric measurements for the 27 patients with CAD are listed in Table 1. The mean resting global ejection fraction was 64 ± 15%. At the peak heart rate achieved during atrial pacing, the mean ejection fraction fell to 54 ± 20% ($p < 0.001$).

Segmental wall motion was quantified for the portion of the ventricular perimeter in the right anterior oblique projection expected to be affected by the ste-

notic artery; the anterobasal or anterior wall for lesions in the left anterior descending and diaphragmatic or posterobasal segments for patients with right CAD. For the wall section affected by the stenotic artery, the mean segmental radial area shortening was 60 ± 22% at rest; during pacing, this value decreased to 48 ± 28% ($p < 0.01$). This segmental wall motion response to pacing was significantly different from the increase observed in the segmental area shortening of patients without CAD (from 61 ± 11% at rest to 79 ± 9% during peak pacing, $p < 0.001$).

The correlations between percent diameter narrowing or minimal lumen diameter and global ejection fraction or segmental radial wall motion are demonstrated in Figures 2 through 6. The percent diameter narrowing correlated moderately with the change in global ejection fraction from rest to peak pacing rate ($r = -0.41$). There was a similar correlation between percent diameter narrowing and the change in segmental radial wall motion ($r = -0.44$) (Figure 2). The determination of minimal lumen diameter yielded a closer correlation with the change in global ejection fraction ($r = 0.61$). However, the closest correlation was between the minimal lumen diameter and the change in segmental radial wall motion: $r = 0.78$ (Figure 3). The effect of atrial pacing in patients with CAD was compared with the effect of anterior and diaphragmatic segmental wall motion in the 10 normal subjects (Figure 4).

The relation between minimal lumen diameter and change in ejection fraction due to atrial pacing also was categorized as shown in Figure 5. In this figure, the results in the 10 normal subjects are compared with the patients whose primary stenoses were divided between those with a minimal diameter ≤1.5 mm (17 patients) and those with >1.5 mm (10). A minimal lumen diameter ≤1.5 mm tended to separate those patients who had a positive outcome in their atrial pacing study (defined as >4% fall in ejection fraction) from those who had a normal response ($p < 0.001$). A similar analysis of the relation between minimal lumen diameter and change in segmental radial wall motion is

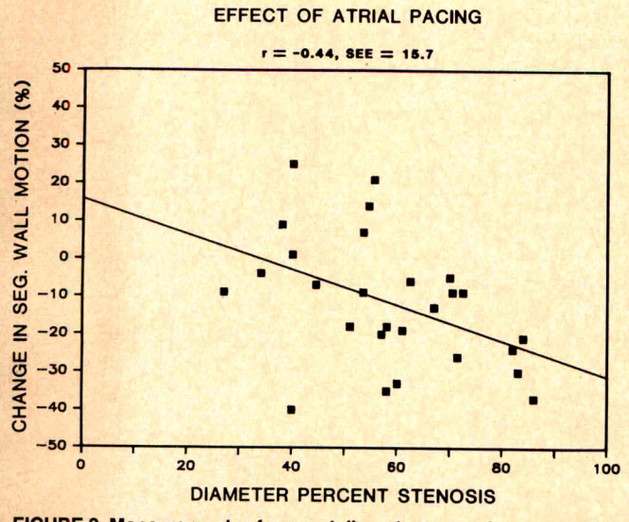

FIGURE 2. Measurements of percent diameter narrowing correlated moderately ($r = -0.44$) with the change in segmental (SEG) wall motion from rest to peak pacing. The primary stenosis in each of the 27 patients with coronary disease was measured and compared with the effect of atrial pacing on the corresponding wall segment. SEE = standard error of the estimate.

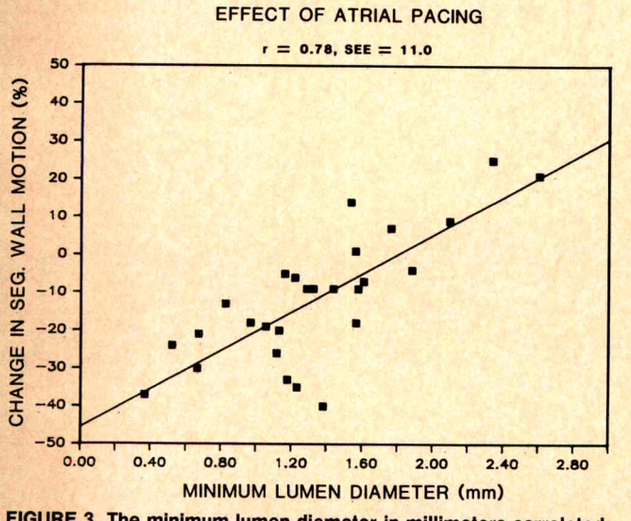

FIGURE 3. The minimum lumen diameter in millimeters correlated more closely with the change in segmental (SEG) wall motion ($r = 0.78$) than did measurements of percent diameter narrowing over a wide range of mild to severe stenoses. SEE = standard error of the estimate.

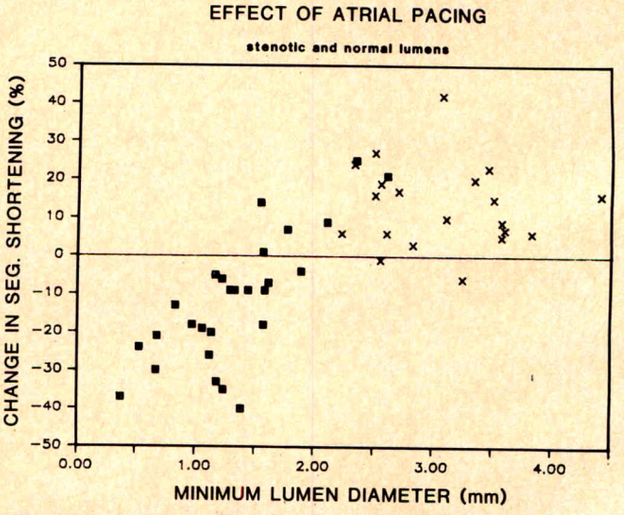

FIGURE 4. The effect of atrial pacing in 27 patients with coronary disease (■) and in 10 subjects with angiographically normal coronary arteries (×) is demonstrated. The measurement of the stenotic lumen or the normal arterial diameter in normal subjects is compared with the effect of pacing on the change in segmental (SEG) wall motion shortening.

shown in Figure 6 for the segmental areas perfused by the left anterior descending coronary artery and in Figure 7 for the areas perfused by the right coronary artery. A minimal arterial diameter of ≤1.5 mm tended to identify those patients likely to have an abnormal response in segmental wall motion during atrial pacing. The normal response to pacing revealed a mean increase in segmental area shortening of 18 ± 11% in the area perfused by the left anterior descending arery and 8 ± 9% in the area perfused by the right coronary artery ($p < 0.05$). The minimal lumen diameter of ≤1.5 mm significantly separated the patients with abnormal responses for both the right coronary artery and left anterior descending artery. However, there was some overlap among patients with left anterior descending artery narrowing between 2.2 and 1.6 mm. Moreover, there was no difference from normal segmental motion in the patients with right coronary artery narrowing between 2.2 and 1.6 mm.

Discussion

Assessment of the severity of coronary artery narrowing is made primarily by angiographic determination of the percent of diameter narrowing relative to an assumed normal portion of the artery. This determination may be misleading for several reasons. Of greatest importance, pathologic studies have demonstrated that atherosclerosis is a diffuse process and even when the angiogram only demonstrates a single stenosis, <25% of the length of the arteries will be free of disease and truly normal.[3,12] In addition, stenoses commonly occur at bifurcations so that it may be difficult to identify a normal proximal portion of the same arterial segment. Consistent with these observations, the study of White et al[13] reported that measurements of percent diameter narrowing correlate very poorly with a physiologic assessment of stenosis severity determined by hyperemic flow response after temporary coronary occlusion during open heart surgery. Legrand and coworkers[14] found a similar poor correlation between mea-

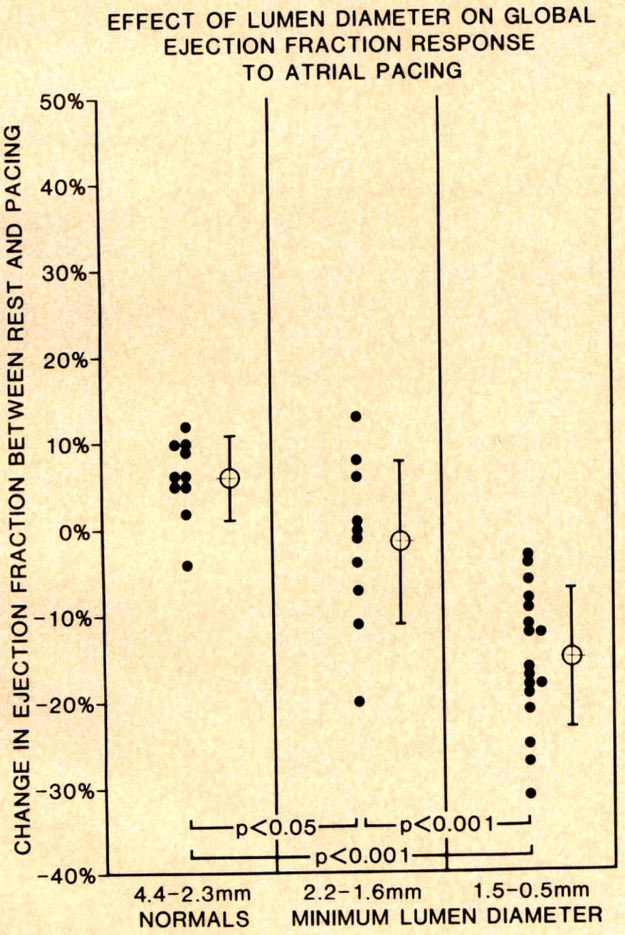

FIGURE 5. The 27 primary stenoses were separated into 2 groups—those with lumens from 0.5 to 1.5 mm and those from 1.6 to 2.2 mm. All were compared with normal lumen dimensions (2.3 to 4.4 mm) to assess the effect of atrial pacing on global ejection fraction. Coronary arteries with minimal lumen diameters <1.5 mm manifested a significant reduction in ejection fraction during pacing.

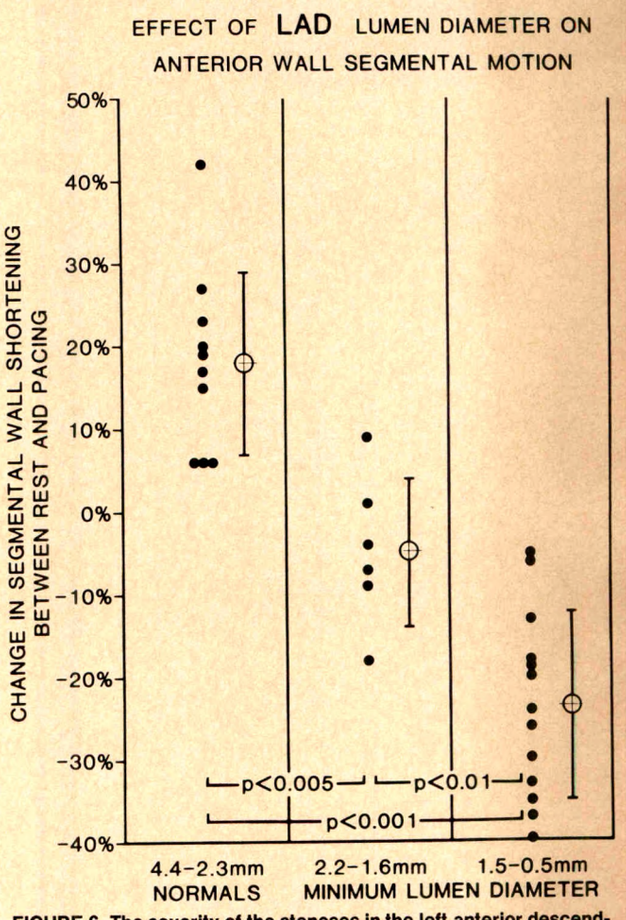

FIGURE 6. The severity of the stenoses in the left anterior descending (LAD) artery demonstrated a progressively impaired response to atrial pacing as measured by the change in segmental anterior wall shortening. The group of patients with a minimal lumen diameter of 1.5 mm or less had a more severe functional response to stress induced by atrial pacing.

surements of percent stenosis and coronary blood flow reserve, as measured by digital flow maps after a hyperemic stimulus.

For these reasons, percent diameter narrowing measurements are flawed as a quantitative method of assessing the severity of CAD. In addition, there is frequent disagreement between observers about the severity of a stenosis[15,16] and it has been suggested that minimum lumen dimensions (either cross-sectional area or linear diameter) would be preferable to using percent diameter narrowing to assess the severity of CAD.[17] Harrison et al found that the minimal lumen diameter correlated better with the hyperemic flow velocity response after 20 seconds of occlusion of the left anterior descending artery.[17] Our data, using the changes in wall motion during atrial pacing in conscious patients, are very similar to their results. In addition, both studies found that an arterial diameter of <1.5 mm was predictive of an abnormal physiologic response. Our data extend these findings to the right coronary artery as well as the left anterior descending. In addition, the data show that measurements of minimal lumen dimensions predict clinical results better than does percent diameter narrowing.

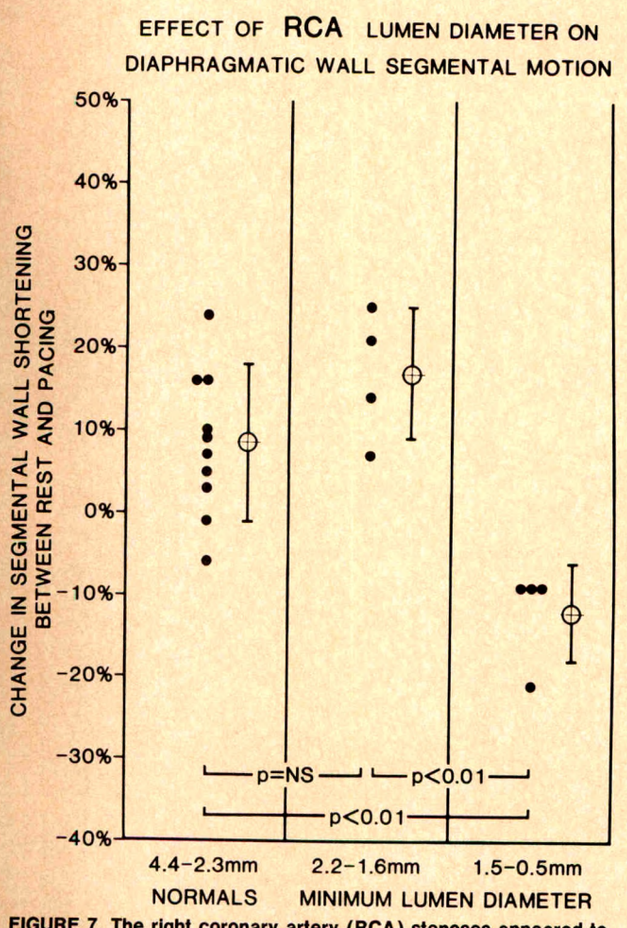

FIGURE 7. The right coronary artery (RCA) stenoses appeared to have a higher threshold than the left anterior descending stenoses for demonstrating a functional impairment to atrial pacing as manifested by a reduction in segmental wall motion. Only stenoses of 1.5 mm or less had a significant response to atrial pacing.

In the present study, atrial pacing stress tests were used as a functional assessment of stenosis severity for comparison with coronary angiographic determinations of stenosis severity.[18,20] In the 27 patients with CAD, measurements of percent diameter narrowing and lumen diameter by edge detection or videodensitometry correlated closely (r = 0.94). Both percent diameter narrowing and minimal lumen diameter correlated with the change in global ejection fraction (r = −0.41 and r = 0.61, respectively). However, it was recognized that the correlation may have been reduced when using global ejection fraction as the measured parameter because the myocardial wall supplied by the normal nonstenotic segments may compensate for diminished motion in the affected myocardium. Localized segmental wall motion was analyzed to isolate the effect of ischemia due to a specific stenosis. The result was a correlation of percent diameter narrowing with segmental wall motion (r = −0.44), similar to that obtained with global ejection fraction (r = −0.41). This result may be explained because percent diameter narrowing is a relative number that does not truly represent the functionally effective resistance to coronary flow. The Pouiselle equation for laminar flow indicates that resistance to flow is inversely proportional to the fourth power of the radius. Thus, a 50% reduction of a 2-mm vessel will have a much greater resistance to flow than a 50% reduction in a 4-mm vessel. When the effect of atrial pacing on segmental radial wall motion was analyzed, there was a clear difference between the 2 methods of measurement of CAD. Whereas percent diameter narrowing was correlated with segmental wall motion with a coefficient of r = −0.44, minimum lumen diameter correlated much more closely (r = 0.78, p <0.05). The improved correlation suggests that the lumen diameter predicts more accurately the functional impairment induced by pacing because the absolute diameter is more directly related to the resistance to flow than percent narrowing.

With regard to the amount of narrowing, our data indicated that the narrowing of an epicardial coronary artery to a diameter <1.5 mm increased the likelihood of a functional impairment induced by atrial pacing in the myocardium supplied by the narrowed artery. Narrowing of the artery to <1.5 mm in diameter increased the probability of a positive study both by global ejection fraction and segmental wall motion. Thus, a minimum lumen diameter <1.5 mm may be useful as a predictor of which patients will be symptomatic during stress.

As demonstrated in Figure 3, there was a close linear correlation between the minimal lumen diameter and the affected segmental wall motion for the patients with CAD. As the stenotic lumen diameter increased, the effect on wall motion leveled off into the range of normal subjects. Our data emphasize the finding that patients with mild disease may not have a functional impairment induced during stress. An exact linear relation between lumen diameter and functional impairment should not be expected because other

influences such as the length of coronary narrowing, vasomobility and the presence of sequential stenoses also impede blood flow.[21-23]

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Recruitment and Baseline Description of Patients in the Cardiac Arrhythmia Pilot Study

THE CARDIAC ARRHYTHMIA PILOT STUDY (CAPS) INVESTIGATORS*

The Cardiac Arrhythmia Pilot Study tested the feasibility of performing a large-scale study to evaluate the effect of therapy of ventricular arrhythmias after acute myocardial infarction (AMI). Ten clinical sites identified patients with ≥10 ventricular premature complexes (VPCs)/hour, recorded 6 to 60 days after AMI in patients with an ejection fraction >0.20. Patients were randomized to receive 1 of 5 agents: encainide, flecainide, imipramine, moricizine or placebo. Successful therapy was defined as ≥70% suppression of VPCs and >90% suppression of runs of ventricular tachycardia. Randomization to a second agent occurred if a patient did not achieve adequate suppression with the initial agent. Patients initially randomized to placebo continued to receive placebo. Patients were evaluated at 3-month intervals for the next year. Of 30,763 patients screened, 10,734 (35%) were younger than 70 years old and had a qualifying AMI. A Holter recording was obtained in 3,957 patients, of whom 871 (22%) had qualifying arrhythmias and 687 were eligible. Of the 687 eligible patients, 502 (73%) were randomized. Mean age of enrolled patients was 59 years. One-half of patients were randomized within 1 month after AMI. Mean ejection fraction was 0.45, with 175 (35%) patients having an ejection fraction <0.40. On baseline drug-free recording, 173 (35%) patients had <30 VPCs/hour; 149 (30%) between 30 and 100/hour and 180 (36%) ≥100/hour. At least 1 run of ventricular tachycardia was seen in 172 (34%) patients. Drugs taken at baseline were similar in all groups with 116 (23%) patients taking digitalis, 161 (32%) taking diuretics, 203 (41%) taking β blockers and 200 (40%) taking calcium antagonists. Slightly more patients, 53 (51%), randomized to flecainide were taking calcium antagonists. No significant relation was noted between baseline VPC frequency and ejection fraction, but baseline VPC frequency was correlated with heart rate, arrhythmia noted before AMI and right bundle branch block. As expected, a high ejection fraction correlated with lower peak creatine kinase values, an inferior location of the infarct and fewer signs of congestive heart failure. At baseline, at least 1 adverse symptom was volunteered by 192 (39%) patients. The most common symptoms were unusual tiredness or fatigue, heart beating fast or skipping beats or headache. In this study, over 20 age- and AMI-eligible patients were identified to obtain each randomized patient. The randomization process successfully distributed baseline variables across drug groups.

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One patient group identified as having a high risk of sudden cardiac death in the U.S. is the post-acute myocardial infarction (AMI) group.[1-3] There are approximately 350,000 patients discharged from the hospital with an AMI as the primary diagnosis each year in this country. The cumulative risk for cardiac death in the year after AMI is about 10%. Early studies suggested that the major factor in determining the risk of death in the year after AMI is left ventricular function,[4] but it has become apparent that ventricular arrhythmias constitute an independent predictor of death.[1,5,6]

Despite attempts to show that suppression of ventricular premature complexes (VPCs) after AMI might be beneficial, no study to date has achieved this goal.[7] The Cardiac Arrhythmia Pilot Study (CAPS) was implemented to address a number of issues important for the optimal conduct of such a trial, and, indeed, provide information as to whether such a trial is even feasible. Important issues included: (1) determining screening processes that would allow sufficient quantities of eligible patients to be identified and recruited; (2) evaluating day-to-day arrhythmia variability, as well as trends over time; (3) determining the feasibility of using arrhythmias detected and quantified by means of 24-hour ambulatory electrocardiograms[8] as measures of drug efficacy for dose titration; (4) assessing whether an appropriate (sufficiently effective and safe) drug existed; (5) determining the natural course of arrhythmias in untreated (placebo) patients; and (6) measuring stress and behavior in order to make recommendations for use of selected instruments in a full-scale trial.

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Address for reprints: Alfred P. Hallstrom, PhD, CAPS Coordinating Center, University of Washington, 1107 Northeast 45th, Room 505, Seattle, Washington 98105.

* See Appendix for the CAPS investigators.

The design of the pilot study was described elsewhere.[9] Briefly, CAPS comprised 10 centers (Figure 1) that enrolled 502 patients in the early post-AMI period (6 to 60 days) who had ≥10 VPCs/hour and left ventricular ejection fractions of >20%. Patients were stratified by ejection fraction (≤40% and >40%) and randomized to 1 of 5 treatment arms (4 active and 1 placebo). This article describes the recruitment process and characteristics of the patient population enrolled.

Recruitment

The CAPS patients were recruited primarily from coronary care units at participating hospitals, but patients referred from other hospitals, clinics and private physicians were also included. All potential patients were entered on screening logs at enrolling CAPS hospitals. Because of the investigational nature of 3 of the CAPS drugs, numerous criteria could exclude a patient from the randomized study (Table I). The limited experience with these agents in patients with severe ventricular dysfunction led to the exclusion of patients with ejection fraction ≤0.20.

The screening process to determine patient eligibility included several steps. The first was a patient interview, physical examination and laboratory tests to determine that the patient was not ineligible because of any general exclusions (Table I). If no general exclusions applied, documentation of the myocardial infarction as a CAPS myocardial infarction by electrocardiogram, enzyme results or both was the next step. If a CAPS AMI was documented, the third step was a 24-hour ambulatory electrocardiogram obtained at least 6 days, and not more than 60 days, after the AMI. Minimal qualifying arrhythmia (≥10 VPCs/hour, ≥5 runs of 3 to 9 ectopic beats at a rate ≥100/min or both) with no excluding arrhythmia criteria must have been present. Finally, the ejection fraction was measured, either by radionuclide studies or angiography, no sooner than 48 hours after the AMI, with an ejection fraction of ≤0.20 excluding the patient. The steps in screening could proceed in a different order, but all 4 steps were necessary.

Because ectopy may continue to increase during the first 6 weeks or longer after AMI, if a screened patient did not have qualifying arrhythmia on the first 24-hour ambulatory electrocardiogram, the electrocardiogram could be repeated once, within 60 days of the qualifying AMI, with a second 24-hour ambulatory electrocardiogram. However, no patient could be randomized if 2 or more 24-hour electrocardiograms showed less than the minimal qualifying arrhythmia.

For all patients ineligible for enrollment, the reason or reasons for exclusion were recorded on screening logs at each enrolling hospital, with a separate log recording detailed information on the subset of patients eligible for randomization. This log included reasons that eligible patients were not randomized.

Early in the study it was assumed that ineligible patients were excluded because of multiple exclusion criteria. Usually only 1 reason for ineligibility was recorded on the screening log for each patient not enrolled. In order to ensure identification of any criteria that might be excluding a significant number of patients and to determine the prevalence of multiple criteria for exclusion, a special screening project was carried out. Seven sites participated, recording all reasons for exclusion for at least the first 50 patients who were age eligible and had a CAPS-defined AMI. Of the sample of 669 screened patients not excluded because of age or no AMI, 585 patients (87.4%) had only 1 exclusion recorded, 68 (10.2%) had 2 exclusions and only 16 (2.4%) had 3 or more exclusions listed.

At the end of the recruitment period, 30,763 patients had been screened at 27 hospitals represented by the 10 clinical sites. Figure 2 depicts the number of patients excluded at each step in the screening process. Of the 30,763 patients screened, 17% were excluded because they were age 75 or older, and 48% were excluded because they did not have an AMI according to the CAPS criteria. Thus, 35% of the original number screened were not excluded by 1 or the other of these 2 major criteria. Because of other clinical exclusions, patient/physician reticence or logistical problems, 67% of age- and AMI-eligible patients were not monitored by 24-hour electrocardiogram while 3,957 (37%) were. Of the latter, 18% had at least 10 VPCs/hour on the initial screening 24-hour ambulatory electrocardiogram. From this pool of 717 patients, 23% were excluded, leaving 554 (77%) eligible for enrollment. A total of 391, or 71%, of these eligible patients with ≥10 VPCs on the first screening electrocardiogram were randomized.

Of 3,240 patients with <10 VPCs/hour on their initial screening 24-hour electrocardiogram, 701 (22%) were rescreened, and of these, 154 (22%) had ≥10 VPCs/hour. Of the rescreened patients 133 (86%) were eligible for randomization, and 111 (83%) of the eligi-

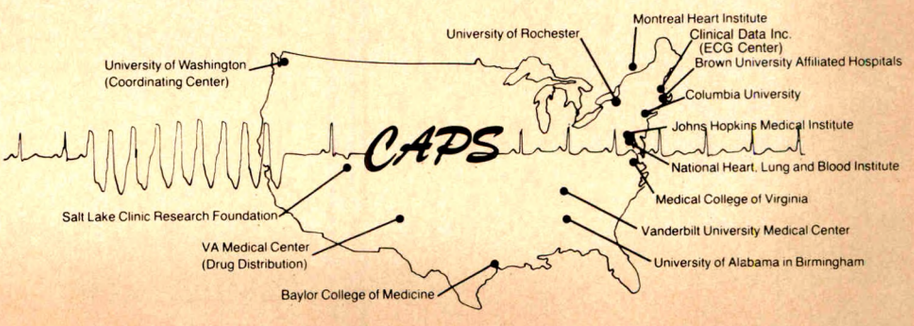

FIGURE 1. Sites for the Cardiac Arrhythmia Pilot Study.

TABLE I Exclusion Criteria for Patients Who Were Not Excluded by Age, Myocardial Infarction or Ejection Fraction

History and clinical
Female with child-bearing potential
Any significant malignancies or other life-threatening disease(s) (other than congestive heart disease) that are likely to be fatal within a 2-year period
Persistent systolic blood pressure ≥180, diastolic blood pressure ≥120 mm Hg, or both
Systolic blood pressure ≤80 and/or a diastolic blood pressure ≤50
NYHA classification class IV (either angina or congestive heart failure)
Clinically significant preexisting nonischemic cardiac condition which is symptomatic or requires treatment (i.e., rheumatic valvular disease, primary cardiomyopathy, mitral valve prolapse syndrome)
Known nonatherosclerotic cause of myocardial infarction
Clinically significant cerebrovascular disease
Creatinine ≥2.5 mg/dl
History of portal hypertension, ascites, portal caval shunt or variceal bleeding
Biopsy-proven cirrhosis
Chronic active hepatitis
Serum glutamic pyruvic transaminase (alanine aminotransferase) or alkaline phosphatase ≥ twice the upper limit of normal
Seizure disorder
Hyperthyroidism
History of narrow-angle glaucoma
Symptomatic urinary tract obstruction (if male)
Electrocardiogram criteria
Ventricular tachycardia ≥10 consecutive beats at a rate of >100 beats/min noted ≥6 days post-myocardial infarction onset
Ventricular fibrillation noted ≥6 days post-myocardial infarction onset
Ventricular tachycardia ≥10 complexes or ventricular fibrillation on graded exercise test done post-myocardial infarction
QRS >0.14 seconds noted ≥6 days post-myocardial infarction onset
Wolff-Parkinson-White syndrome at any time or atrial fibrillation at time of screening requiring treatment by other than digoxin or precluding 18 hours of interpretable ventricular electrocardiogram recording
Sinus pause ≥2.5 seconds noted ≥6 days post-myocardial infarction onset
Second-degree Mobitz II block or third-degree AV block noted ≥6 days post-myocardial infarction onset
PR interval >0.30 seconds noted ≥6 days post-myocardial infarction onset
Symptomatic sinus node dysfunction
Heart rate ≤30 asleep or ≤40 awake for a period lasting >1 minute noted ≥6 days post-myocardial infarction onset
Myocardial infarction ≤8 days after coronary artery bypass graft
Left bundle branch block pattern
Drug therapy
Previous serious adverse effect from 1 of the drugs under investigation
Use of drugs that are potentially arrhythmogenic, e.g., monoamine oxidase inhibitors, inhalant bronchodilators
Taking drugs with antiarrhythmic effect, such as anticonvulsants or tricyclic antidepressants
Use of drugs that interfere with study drug excretion
Angina likely to require manipulation of β blocker or calcium antagonist during Cardiac Arrhythmia Pilot Study dosing
Any phenothiazine preparation needed (except sporadic use of chlorpromazine, prochlorperazine or promethazine)
Parkinsonism being treated with anti-Parkinson drugs
Miscellaneous
Psychologically unfit to participate in the study
Alcoholic or other "noncomplier," or unable to participate effectively in the evaluation of potential side effects and symptoms
Permanently functioning ventricular pacemaker
Geographically inaccessible

AV = atrioventricular; NYHA = New York Heart Association.

ble patients were randomized. Had only 1 screening 24-hour ambulatory electrocardiogram been done, 19% of the eligible patients and 22% of the randomized patients would have been lost to the study. Finally, of the 3,957 patients who were screened for CAPS with at least one 24-hour ambulatory electrocardiogram, 17.4% or 687 patients were eligible and 12.7%, 502 patients, were randomized. Patients who qualified on a second screening 24-hour ambulatory electrocardiogram were required to obtain a third 24-hour ambulatory electrocardiogram recording as a baseline for drug/dose finding.

Of all eligible patients, including those who were rescreened, 185 (27%) were not randomized. For 6% of these 185 patients, the protocol time window elapsed before the patient could be randomized. For 13%, the patient's private physician refused approval. The other reasons given were categorized as inconvenience of

TABLE II Distribution of Baseline Variables by Treatment Arm

Variable		Encainide-Imi/Mor (n = 99)*	Flecainide-Imi/Mor (n = 103)	Imipramine-Enc/Flec (n = 102)	Moricizine-Enc/Flec (n = 98)	Placebo-Placebo (n = 100)	Overall (n = 502)	One-Way ANOVA p Value
Age	Mean	59	59	59	59	60	59	0.99
	SD	9	9	9	9	10	9	
	Max	74	74	74	73	74	74	
	Min	33	33	39	21	33	21	
Cases (%)								
<55		25	27	29	30	29	28	
55–64		45	38	39	43	41	41	
65–74		29	35	31	28	30	31	
Standing heart rate (beats/min)	Mean	77	78	81	81	82	80	0.07
	SD	13	16	15	15	16	15	
	Max	112	122	114	120	124	124	
	Min	48	52	55	50	48	48	
Standing systolic blood pressure (mm Hg)	Mean	116	117	120	115	117	117	0.41
	SD	18	20	21	18	17	19	
	Max	190	190	210	178	180	210	
	Min	80	78	80	82	77	77	
Diastolic blood pressure (mm Hg)	Mean	75	75	76	74	77	76	0.25
	SD	10	11	11	11	11	11	
	Max	110	108	100	105	108	110	
	Min	50	54	56	56	44	44	
Cardiothoracic ratio (%)	Mean	48	49	49	49	50	49	0.39
	SD	5	7	5	7	6	6	
	Max	66	68	70	73	71	73	
	Min	38	36	37	38	33	33	
Ejection fraction (%)	Mean	45	45	46	44	45	45	0.82
	SD	12	13	15	14	12	13	
	Max	74	78	84	88	70	88	
	Min	21	21	21	21	21	21	

* Number of patients randomized, excluding protocol violations.

ANOVA = analysis of variance; Enc = encainide; Flec = flecainide; Imi = imipramine; Mor = moricizine; Max = maximum; Min = minimum; SD = standard deviation.

the scheduled visits (too many visits, difficulty in traveling to the site), 16%; patient unwillingness to extend hospitalization to initiate the CAPS drug or to be rehospitalized to initiate the second drug, 11%; dislike of research trials in general, 16%; other physical or anxiety problems, 11%; concern over the listed adverse effects, 3%; denial of the seriousness of the illness, 3%; and no reason given, 21%.

For randomized patients, although the mean time from qualifying AMI to 24-hour electrocardiogram was 26 days over all sites, means at individual sites varied from 16 to 33 days. The mean time from first to second screening 24-hour electrocardiogram was 28 days and varied between sites from 21 to 36 days. The mean time from qualifying 24-hour electrocardiogram to randomization was 4.7 days over all sites, and varied from 3.0 to 6.1 days at individual sites. These recruitment times did not change over the course of the study.

Baseline Descriptions

Enrollment began July 25, 1983, and ended on August 21, 1985, during which time 502 patients were enrolled. The patients included 418 men with a mean age of 59 ± 9 and 84 women with mean age of 61 ± 9 years. Total enrollment by month showed a moderate learning curve and slight peaks in mid-winter. Twenty-nine percent of patients were randomized by the end of the second week after AMI, 15% in the third

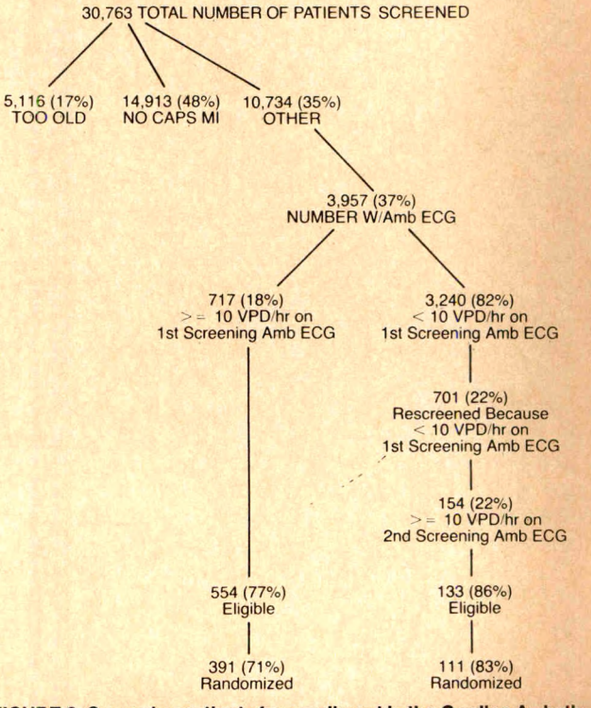

FIGURE 2. Screening patients for enrollment in the Cardiac Arrhythmia Pilot Study. ECG = electrocardiogram; MI = myocardial infarction; VPD = ventricular premature depolarizations.

TABLE III Distribution of Baseline Behavioral and Psychosocial Variables by Treatment Arm

Variable		Encainide-Imi/Mor (n = 68)*	Flecainide-Imi/Mor (n = 69)	Imipramine-Enc/Flec (n = 70)	Moricizine-Enc/Flec (n = 73)	Placebo-Placebo (n = 71)	Overall (n = 351)	One-Way ANOVA p Value
Social support	Mean	23	24	23	22	23	23	0.33
	SD	3	2	3	3	3	3	
	Max	26	26	26	26	26	26	
	Min	11	13	12	14	12	11	
Speilberger state anxiety	Mean	36	35	36	36	35	36	0.91
	SD	10	11	12	10	11	11	
	Max	60	71	60	72	67	72	
	Min	20	20	20	20	20	20	
Beck depression inventory	Mean	8	8	10	8	9	8	0.37
	SD	6	6	7	6	7	6	
	Max	24	34	37	28	33	37	
	Min	0	0	0	0	0	0	
Marlowe-Crowne social desirability	Mean	20	20	19	19	21	20	0.20
	SD	7	6	6	6	5	6	
	Max	32	31	30	31	31	32	
	Min	4	6	3	8	4	3	
Speilberger trait anxiety	Mean	39	39	40	39	38	39	0.71
	SD	9	8	9	7	8	8	
	Max	57	60	65	61	63	65	
	Min	4	26	25	26	26	4	
Speilberger anger expression scale	Mean	19	20	21	20	19	20	0.76
	SD	7	6	7	9	8	7	
	Max	40	41	42	47	40	47	
	Min	6	9	7	7	5	5	
Bortner type A behavior	Mean	174	169	181	177	177	176	0.46
	SD	36	42	39	38	44	40	
	Max	254	262	287	288	278	288	
	Min	84	14	67	93	14	14	
Profile of mood score	Mean	11	12	18	13	15	14	0.65
	SD	30	34	32	30	36	32	
	Max	108	151	106	93	125	151	
	Min	−36	−34	−36	−38	−34	−38	

* Number of patients randomized with social support data reported, excluding protocol violation.
Abbreviations as in Table II.

week, 7% in the fourth week and 49% 4 to 8 weeks after AMI.

Descriptive statistics of selected factors for patients grouped by initial drug assignment and for all patients are shown in Tables II, III and IV. Overall, the mean ejection fraction was 0.45 and 175 (35%) of the patients fell in the low (<0.40) ejection fraction stratum. Baseline rates of VPCs of <30/hour were seen in 171 (35%) patients and 180 (36%) had rates ≥100 VPCs/hour. At least 1 run of asymptomatic ventricular tachycardia (VT) of length 3 to 9 VPCs at a rate of ≥100 beats/min was observed in 172 (34%) of the baseline 24-hour electrocardiograms. The 27 (5.4%) patients with baseline VPCs/hour rates of <10 consist of 1 patient who qualified only on the basis of runs, of 21 patients who had <10 VPCs/hour on an initial screening 24-hour electrocardiogram and hence were required to have a baseline (third recording) obtained after having ≥10 VPCs/hour on a second screening electrocardiogram, and of 5 patients for whom the baseline was reestablished during the drug/dose finding phase. More women than men had a family history of angina (38 [51%] vs 147 [38%], p <0.03), sustained systemic hypertension (34 [41%] vs 125 [30%], p <0.05), diabetes mellitus (21 [25%] vs 60 [14%], p <0.015) and had never smoked cigarettes (26 [31%] vs 60 [14%], p <0.001).

Not all factors are uniformly distributed across initial treatment groups. Of note is the lower incidence of cardiac enlargement in 21 (23%) of patients assigned to encainide-imipramine/moricizine limb; this occurred in 35 (39%) of patients assigned to placebo. With the possible exception of calcium antagonists there were no significant differences in the distribution of drugs taken at baseline across drug groups. Overall 116 (23%) of the patients were taking digitalis, 161 (32%) were taking diuretics, 203 (41%) were taking β blockers and 76 (15%) were taking potassium supplements. Two hundred (40%) patients were taking calcium antagonists; 51% of the patients assigned to the flecainide-imipramine/moricizine limb (the highest) and 34% of the patients assigned to the encainide-imipramine/moricizine limb and to placebo (the lowest).

Twenty-four-hour ambulatory electrocardiogram: The qualifying (usually but not always the baseline used during the drug/dose finding phase) 24-hour ambulatory electrocardiogram was obtained an average of 27 ± 18 days post-AMI and was obtained in-hospital in 60% of the patients. The usable recording time averaged 23 ± 1.6 hours. The electrocardiographic measurements from the 24-hour electrocardiogram were RR 0.79 ± 0.18, PR 0.17 ± 0.03, QRS 0.08 ± 0.02 and QT 0.37 ± 0.05. The average number of VPCs per recording was 3,151 (median 1,167). There was an av-

TABLE IV Percent Distribution of Discrete Baseline Variables by Treatment Arm

Variable	Encainide-Imi/Mor (n = 99)*	Flecainide-Imi/Mor (n = 103)	Imipramine-Enc/Flec (n = 102)	Moricizine-Enc/Flec (n = 98)	Placebo-Placebo (n = 100)	Overall (n = 502)	Chi-Square p Value
Male	85	82	84	85	81	83	0.91
Non-white	24	24	24	14	21	22	0.38
Before AMI, history of							
Hypertension	30	34	31	29	35	32	0.83
Diabetes	17	24	9	13	17	16	0.04
Congestive heart failure	7	4	8	6	6	6	0.81
Probable angina (≥7 days before AMI)	48	50	49	45	42	47	0.75
Prior AMI	27	35	26	31	31	30	0.65
Cardiac surgery	12	18	15	15	11	14	0.61
During month prior to AMI							
Digitalis	9	9	13	17	7	11	0.15
Diuretics	24	33	28	22	31	28	0.42
Beta blockers	16	21	26	16	24	21	0.28
Calcium antagonists	13	16	9	10	6	11	0.22
Antiarrhythmic	4	7	3	7	2	5	0.31
Early family history of angina or AMI	33	35	44	45	28	37	0.06
Cigarette smoking							
Present	35	23	33	35	30	31	0.37
Former	48	59	53	50	48	52	0.45
Never	17	17	14	15	22	17	0.62
For the CAPS AMI							
Transmural	68	73	68	69	69	69	0.95
Nontransmural	32	27	32	31	31	31	0.95
VF before day 6	8	8	5	5	5	6	0.78
Treated CHF	17	17	13	27	19	19	0.16
Streptokinase	13	17	18	14	17	16	0.90
PTCA	7	9	6	4	7	7	0.75
Hypotension	3	5	1	4	8	4	0.14
Pulmonary edema	8	6	9	7	3	7	0.50
Drugs at baseline							
Digitalis	18	25	26	26	20	23	0.57
Diuretics	33	35	27	36	30	32	0.71
Beta blockers	46	36	43	37	41	41	0.56
Calcium antagonists	34	51	42	38	34	40	0.06
Potassium supplements	16	16	14	12	18	15	0.80
At baseline							
EF <30	12	14	17	22	9	15	
30–39	23	23	18	12	24	20	0.30
40–49	30	26	23	26	30	27	
50–59	22	25	24	29	22	24	
≥60	12	12	20	11	15	14	
Number of runs of length 3 to 9†							
None	62	65	62	72	68	66	
1	21	12	24	8	17	16	
2–5	12	11	9	10	8	10	0.14
≥6	5	13	6	9	7	8	
VPCs/hour:†							
<10	8	6	4	5	4	5	
10–29	38	30	25	27	26	29	
30–99	23	33	32	30	30	30	0.27
100–299	16	14	28	25	20	21	
≥300	14	18	11	14	20	15	
Cardiac enlargement	23	24	24	30	39	28	0.10

* Number of patients randomized, excluding protocol violations.

† Based on the final baseline established for titration decisions.

AMI = acute myocardial infarction; CAPS = Cardiac Arrhythmia Pilot Study; CHF = congestive heart failure; EF = ejection fraction; PTCA = percutaneous transluminal coronary angioplasty; Runs = 3 to 9 consecutive ventricular premature depolarizations at ≥100 beats/min; VF = ventricular fibrillation; VPC = ventricular premature complexes; other abbreviations as in Table II.

erage of 13 runs of length 3 to 9 VPCs at a rate ≥100 beats/min among the 33% of recordings with at least 1 run. Of these, 51% had only 1 run. Because of concern about selection based on extreme observations, a third 24-hour electrocardiogram obtained between qualifying and beginning the drug/dose finding phase was required by protocol for the 111 patients who qualified at a second (and not at the initial) screening. Among the 96 patients for whom a third recording was done (the protocol was not adhered to in 15 instances), data from both 24-hour electrocardiograms were submitted for 87 patients. In these, the spontaneous decrease in VPCs/hour between the successful screening and the baseline recording averaged 8.3 ± 165.4 and the inter-

val between these 2 recordings averaged 4.6 ± 2.1 days. The baseline rate was <10 VPCs/hour for 21 of the 87 patients. The baseline ultimately used for evaluation during the drug/dose finding phase of the study was the VPC/hour rate obtained on the last 24-hour ambulatory recording taken while the patient was off antiarrhythmic therapy before the end of drug/dose finding. This was different from the qualifying or pretitration baseline recording for 60 patients for whom the mean qualifying rate was 122 ± 191 VPCs/hour while the baseline rate was 238 ± 249 VPCs/hour.

Radionuclide ventriculography: Baseline radionuclide ventriculography was performed in 86% of all randomized patients yielding a mean left ventricular ejection fraction of 0.44 ± 0.13 and a mean right ventricular ejection fraction of 0.37 ± 0.15. Of patients with a radionuclide ventriculogram, regional wall motion studies were conducted in 404/434 (93.1%). Left ventricular motion was quantified in 9 segments, 5 in the anterior or right anterior oblique view and 4 in the left anterior oblique view. Segments were classified as normal, moderately hypokinetic, severely hypokinetic, akinetic, dyskinetic, aneurysmal or unknown. Wall motion was normal in 37% of apical segments and in 52 to 79% of the other segments. Akinetic motion was seen in approximately 10% of segments, most often in the apical region (20%). The ejection fraction determination was made from angiography in the catheterization laboratory for 14% of patients. The mean left ventricular ejection fraction for these patients was 0.51 ± 0.13. For 2 patients, the ejection fraction was done less than 48 hours after the AMI (outside the protocol time window), and for another, the ejection fraction was visually estimated, though not measured, by angiography.

Physical examination: The mean recorded weight was 79.9 ± 15.9 kg for men and 71.4 ± 15.5 for women. Men averaged 174.7 ± 8.0 and women 161.6 ± 7.7 cm in height. Ninety-three percent of the baseline physical examinations were done within the time window (1 day before randomization, up to the day the drug was initiated), and a total of 98% were done more than 5 days post-AMI and before drug initiation. For these, the supine heart rate averaged 73.3 ± 14.1 beats/min and the blood pressure averaged 120 ± 18/75 ± 10 mm Hg. An S_4 sound was commonly found (38%), while carotid bruit (4%), rales (7%), heaves (7%), S_3 sounds (5%) and murmurs (14%) occurred less frequently. Edema of the lower extremities was found in 10% and peripheral pulses were absent or diminished in 25%.

Chest x-ray: The chest x-ray was obtained on average 26 days post-AMI and 4.4 days before randomization, with 7% not done within the required time (at least 48 hours after the AMI, and up to 3 days after randomization). Thirty-eight percent of the patients were taking β-blocking drugs at the time of the chest x-ray, cadiac enlargement was noted in 130 (28%) of the patients, the transverse cardiac diameter averaged 153 ± 20 mm and the cardiothoracic ratio averaged 0.49 ± 0.06.

Blood samples: Ninety-eight percent of the baseline blood samples and 92% of the urine samples were done within the protocol time window (from 1 week before, up to the day of drug initiation). For these patients baseline blood samples were collected on average 2.2 ± 1.5 days before randomization and urine samples on average 0.6 ± 1.5 days. Blood and urinalysis were performed at the on-site hospital laboratories, which were not standardized, but all were certified by professional societies. The percent of measurements declared abnormal (>2 standard deviations from laboratory standards) are as follows: hemoglobin 33%, hematocrit 45%, white count 15%, platelet count 16%, specific gravity 8%, pH 9%, protein (urinalysis) 9%, glucose (urinalysis) 6%, ketones (urinalysis) 3%, sodium 8%, potassium 9%, chloride 15%, bicarbonate 13%, glucose (blood chemistry) 36%, urea nitrogen 18%, bilirubin total 8%, bilirubin direct 26%, alkaline phosphatase 25%, total serum protein 12%, albumin 15%, serum glutamic oxaloacetic transaminase 12%, serum glutamic pyruvic transaminase 15%, creatinine 13% and calcium 15%.

Twelve-lead electrocardiogram: The 12-lead electrocardiogram for baseline was obtained an average of 27 ± 21 days post-AMI and 4 ± 7.9 days before randomization. For patients randomized more than 15 days after the qualifying AMI, another electrocardiogram was required at randomization, and 1% of these baseline electrocardiograms were not done. (All electrocardiograms documenting the qualifying AMI were done.) ST abnormalities were noted in 40% of the patients, with elevation (Minnesota codes 9-2-1, 9-2-2 or 9-2-3) present in 68% of these and depression (Minnesota codes 4-1, 4-2, 4-3 or 4-4) present in 54%. T-wave abnormalities were noted in 85% of the patients. Q waves diagnostic of an AMI were observed in 69% of the patients. The distribution of the location of the AMI were: anterior 45.6%, inferior 39.6% and other 14.7%.

Three extensive baseline data forms were collected, including a socio/demographic form, a history and clinical form (tabulated in Table II) and an adverse effects form.

Socio/demographic form: The patient population was predominantly white (79%) with 17% black, 3% Hispanic and 1% Asian. Most (74%) of the patients were married, with 9% divorced, 10% widowed, 3% separated and 4% single. The average number of people living in the patient's household was 3. Only 13% had fewer than 7 years of education, but 47% had not completed high school. The most common occupation listed was laborer (32%), with 15% described as clerical, 14% as professional, 5% as homemaker and 11% as self-employed. At the time of the AMI episode, 47% were working full-time and 8% part-time and 32% were retired. Only 17% of the patients had never smoked. Although 31% of the patients stated that they were present smokers, fully 60% stated that they had been smoking as recently as the week before admission for AMI. Of those who claimed to be former smokers, over 50% reported quitting since 1981. Change to a less strenuous lifestyle, with reduced ac-

tivity, before the AMI because of health was reported by 29% of patients.

Adverse symptoms: Data on adverse symptoms were obtained at baseline on 98% of patients. At least 1 adverse symptom was volunteered by 192 (39%) of the patients. The most common symptoms volunteered were unusual tiredness or fatigue during ordinary activities (8%), heart beating fast or skipping beats (6%), headache (5%), dizziness or light headedness (5%), restlessness, nervousness (4%), dizziness only upon standing (4%), insomnia or frequent awakening from sleep (3%) and constipation (3%). When symptoms were elicited by asking a response for each specific symptom on the list, the results were similar, although the incidence was higher. Besides the aforementioned symptoms, dry mouth and coldness in hands or feet were frequently (46%) elicited.

Other procedures: Many patients underwent exercise tolerance testing (n = 107), invasive electrophysiologic studies (n = 5), coronary angiography (n = 146), angioplasty (n = 33), thrombolysis (n = 79) coronary artery bypass surgery (n = 67) or some combination of these. The CAPS protocol also included a behavioral stress testing procedure, consisting of a Pac-Man game played under pressure to improve scores in patients with adequate vision and no dominant hand mobility problems. This procedure was performed in 340 (68%) of the patients. Of the 162 instances in which the procedure was not done, 81 were due to referral to a special protocol, 7 to morbidity and the remainder to refusals and scheduling problems. Blood pressures and mean heart rates were obtained during the baseline period and during a stress period, and then during a relaxation period, each approximately 10 minutes long. The mean heart rate increased 2.6 ± 7.0 from 73.8 at baseline to 76.4 during stress and then dropped back to 74.5 beats/min during relaxation. Systolic blood pressure changed 8.0 ± 11.5 from 117.5 to 125.5 and fell back to 117.7 mm Hg. Diastolic blood pressure increased 4.8 ± 10.0 from 75.9 to 80.7 and then returned to 76.9 mm Hg.

Psychologic measures were also obtained when there were no language or reading problems. Comparisons are made for the Bortner type A scale,[10] the Beck depression inventory,[11] the Marlowe-Crowne measure of social desirability[12] and the Spielberger State/Trait Anxiety and Anger Expression Scales.[13,14] These measures were obtained on 351 patients. The Bortner type A scale quantifies factors related to hard-driving traits, time-pressured qualities and competitiveness, but not factors related to anger expression. The results from the CAPS sample, 176 ± 40, were quite similar to the post-AMI English sample, 174 ± 42, enrolled in the United Kingdom Disease Prevention Project.[15] The overall mean was approximately one-half standard deviation below the 200 cutoff on the Bortner for a type A classification. The Beck depression inventory scores appeared to be quite low in the CAPS sample, 8.4 ± 6.5. Based on norms established with psychiatric patients, this suggests that only about 2 to 3% would be expected to exhibit clinical levels of depression. It appears more parsimonious to assume that actual rates of depression were higher, and that psychiatric norms cannot be applied to the CAPS sample.

TABLE V Bivariate Distribution of VPC Frequency and Left Ventricular Ejection Fraction (LVEF)

VPC frequency (in counts per hour)*	LVEF (%) <30	30 <40	40 <50	≥50	Total
<10	0%	1%	1%	3%	5%
10 <30	5%	6%	9%	10%	29%
30 <100	4%	6%	7%	12%	30%
≥100	5%	7%	10%	14%	36%
Total	15%	20%	27%	38%	

* Based on the final baseline established for titration decisions.
VPC = ventricular premature complex.

While there was little evidence of depression, the Marlowe-Crowne scale indicated significant evidence of defensiveness. The mean level for the Marlowe-Crowne scale obtained in the CAPS sample, 19.8 ± 6.0, is at the cutoff for a significant level of defensiveness,[16] similar to a mixed cardiac sample, 19.4 ± 5.7.[17] The trait anxiety, 38.9 ± 8.2, and state anxiety, 35.7 ± 10.9, scores were similar to those observed in another post-myocardial infarction sample.[18] The anger expression data from the CAPS sample, 19.6 ± 7.4, indicated that CAPS patients were not particularly expressive of their anger.

The baseline data shown demonstrate that the randomization process worked well. There was good comparability, for most variables, between treatment groups. Most baseline data were collected within the established time windows, and the various protocol-required measures and procedures were obtained in almost all patients.

Bivariate Relations

Ignoring obvious correlations between weight and height, supine systolic and diastolic blood pressures, heart rate and electrocardiogram measurements, correlations between baseline clinical factors tended to fall into the negligible range (−0.2 to 0.2), while pairwise correlations between the summary measures of behavioral tests at baseline appear to be quite high, especially between trait anxiety and state anxiety (0.63), Beck depression instruments and state anxiety (0.57), and Beck depression instruments and trait anxiety (0.62). Correlations between these behavioral scores and a few important clinical factors (age, ejection fraction, VPC rate, heart rate and blood pressure), as well as reactivity measurements obtained from the behavioral stress test, tended to be negligible with the strongest correlations (−0.04 to −0.17), indicating more psychosocial dysfunction with increasing age.

Because of the prominence of the ejection fraction as a predictor for death,[1,5] and because of the extreme importance of the outcome measure, VPCs per hour, for CAPS, we investigated the relation of these 2 variables to virtually every other variable collected at baseline. The correlation between ventricular premature depolarization frequency and left ventricular ejection fraction was −0.07. The bivariate distribution

is shown in Table V and confirms the lack of any correlation. A *t* test was used as a nominal instrument for measuring significant mean differences of either of these 2 variables on groups determined by baseline dichotomous variables in the first 251 cases. Significance was taken as the nominal 0.165 level. Those variables found to determine groups with significantly differing mean left ejection fraction or VPC frequency for the first 251 patients were submitted to analysis on the second 251 patients, and were considered "significant" if the p value was again <0.165 and the effect was in the same direction. Similarly, a test that the correlation was zero was used to find continuous variables "significantly" related to left ventricular ejection fraction or VPC frequency. The nominal level 0.165 was chosen because if a variable was "significant" in 502 cases at the 0.05 level and was evenly distributed in the first and second 251 cases, the observed level would be 0.165 in each half. On the other hand, if all the variables were independent of the variable of interest, only 1.4% would be expected to be "significant" by chance. Of 170 variables examined, 4 were nominally "significant" with regard to ectopy counts (log[VPC/hr + 1]). These are: atrial heart rate (positively correlated) (p <0.001); use of antiarrhythmics before AMI (positively correlated) (p <0.003); bradycardia <60 (negatively correlated) (p <0.0001) and right bundle branch block (negatively correlated) (p <0.01). Two of these variables were related to heart rate (atrial heart rate and bradycardia recorded on physical examination). The use of antiarrhythmics before the AMI might well be expected to relate to measured frequency after AMI.

Using the same 170 variables, the ejection fraction showed a significant relation to 32. Many of these variables demonstrate an association of higher ejection fraction with location and "size" of infarct, fewer drugs and fewer signs of congestive heart failure. When these 32 variables were submitted to a stepwise regression procedure (BMDP2R) with a selection level of p = 0.10, the factors associated with higher ejection fraction in order of selection were an inferior AMI location, lower atrial heart rate, no prior AMI, absence of Q-waves noted on baseline electrocardiogram, higher supine systolic blood pressure, no history of congestive heart failure before the AMI, absence of diuretic use at baseline, normal white count, creatine phosphokinase within the upper limit of normal, shorter QRS duration noted on baseline electrocardiogram, β blocker use at baseline and percutaneous transluminal coronary angioplasty for this myocardial infarction.

Discussion

CAPS was designed to test the feasibility of performing a large-scale study to evaluate the effect of antiarrhythmic drug therapy for ventricular arrhythmias after AMI. Many patients were screened to identify eligible candidates. Of patients who were age and AMI eligible and who had a screening 24-hour ambulatory electrocardiogram, only 22% had qualifying arrhythmias. Over 20 patients who were age and AMI eligible were identified for each patient randomized. Of 687 eligible patients, 502 (73%) signed informed consent.

This patient population had been truncated to eliminate patients with very low ejection fraction and patients who had few VPCs. One-third of all patients included had at least 1 run of asymptomatic VT. Baseline drug administration was similar in each group, but, by chance, slightly more patients in the flecainide-imipramine/moricizine limb were taking calcium antagonists.

No relation was noted between baseline VPC frequency and the baseline ejection fraction. The selection process eliminated patients with ejection fraction ≤20% and patients with VPC rates <10/hour, and might have obscured the weak association usually found between ejection fraction and VPC rates.[1,5] The frequency of VPCs correlated positively with heart rate and use of antiarrhythmics before AMI, and was correlated negatively with bradycardia and right bundle branch block. The significance tests relating ejection fraction to other variables should be viewed cautiously. Because so many variables were examined, it would be expected that some correlations could have been noted spuriously. However, because of the approach used, it is unlikely that more than 3 or 4 correlations are spurious, and it is likely that several marginally significant correlations were missed. It is reasonable that ejection fraction correlates with measures of myocardial damage and with drug use. The lack of significant associations with VPC frequency may be in part due to the selection process in CAPS and the naturally occurring large variation in these rates. It is also possible, as others have suggested, that ectopy is independent of the baseline variables that are generally collected.

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Appendix: The CAPS Investigators

University of Alabama in Birmingham: Albert L. Waldo, MD,* William J. Rogers, MD,* Richard W. Henthorn, MD, Brian Olshansky, MD, Andrew E. Epstein, MD, Albert Oberman, MD, Mark D. Cohen, MD, Paul Hess, MD. *Coordinators*: Donna Kerns, RN, Terry Glickman, RN.

Baylor College of Medicine: Craig M. Pratt, MD,* J. Alan Herd, MD, Christopher R. Wyndham, MD, Allen Seals, MD, Miguel Quinones, MD, Robert Roberts, MD, Mario Verani, MD, James Young, MD. *Coordinators*: Amy Galloway, RN, Ann Riordan, RN, Pat Carlson, RN, Beth C. Thornton, RN.

Brown University Affiliated Hospitals: Robert J. Capone, MD,* Edward W. Bough, MD, David Ahern, PhD, Michael Follick, PhD, Larry Gorkin, PhD, Abdul H. Khan, MD, Suh-Dong Hahn, MD, Henry Gewirtz, MD, Gregory Macina, MD, Gary Heller, MD, Richard Carleton, MD. *Coordinators*: Kathryn Alberti, RN, Connie Lamore, RN, Denise Tremblay, RN.

Columbia University: J. Thomas Bigger, Jr., MD,* James Coromilas, MD, Francis M. Weld, MD, Elsa-Grace V. Giardina, MD, James A. Reiffel, MD, Donald Kornfeld, MD, Jean Warner, MD, Alan Saroff, MD, Lynne Johnson, MD, Richard Sloan, PhD. *Coordinator*: Robert Stanyon, RN.

Johns Hopkins University: Philip R. Reid, MD,* Lawrence S. Griffith, MD,* Edward V. Platia, MD, Craig Ewart, PhD, Diane Becker, PhD, Bernard Tabaznik, MD, Stephen Pollock, MD, Jeffrey Quartner, MD, Dean Taylor, MD, Michael Keleman, MD, Sheldon Gottlieb, MD, Morton Mower, MD, Michel Mirowski, MD, Nisha Chandra, MD, Raymond Bahr, MD. *Coordinators*: Patricia Pollock, RN, Linda Prinkey, RN, Mary Sullivan, RN, Diana Aarons, RN, Carol Williams, RN.

Medical College of Virginia: David W. Richardson, MD,* Donald W. Romhilt, MD, Andrea Hastillo, MD, Fred D. Robinson, MD, John Herre, MD. *Coordinator*: Barbara Bane.

Montreal Heart Institute: Pierre A. Theroux, MD,* Denis Roy, MD. *Coordinator*: Doris Morissette, RN.

University of Rochester: Toshio Akiyama, MD,* William B. Hood, Jr., MD, Paul N. Yu, MD, William Henion, MD, Gur Adhar, MD, Mark Rosenzweig, MD, James Doling, MD, Robert Easley, MD. *Coordinators*: Laura Butler, Marcia Keller, RN.

Salt Lake Clinic Research Foundation: Allan H. Barker, MD,* Jeffrey L. Anderson, MD, Robert E. Fowles, MD. *Coordinators*: Ellen N. Doran, Joan R. Lutz, RN.

Vanderbilt University: Raymond L. Woosley, MD,* Dan M. Roden, MD, Tobey Barbey, MD, Kirby Primm, MD, Bart Campbell, MD, Kathy Thompson, MD, Lyle Siddoway, MD, Debbie Echt, MD. *Coordinators*: Mary DeLoache, RN, Laurie Hays, RN, Tina Thomas, RN, Leslie Jared, RN, MSN.

Ambulatory Electrocardiogram Reading Center: Clinical Data Inc., Israel M. Stein, MD,* Carolyn O'Connor.

Drug Distribution Center: VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center: Dennis Toussaint, RPh, MS, Clair Haakenson, RPh, MS.

Coordinating Center, University of Washington: Alfred P. Hallstrom, PhD,* Mary Jo Gillespie, MS, H. Leon Greene, MD.

Project Office, National Heart, Lung and Blood Institute: Lawrence Friedman, MD, Joel Verter, PhD, Salim Yusuf, MD, C. Eugene Harris, Eleanor Schron, RN, MS.

* Principal investigator.

Prevalence and Significance of Atrial Fibrillation in Coronary Artery Disease (CASS Registry)

AIRLIE CAMERON, MD, MILES J. SCHWARTZ, MD, RICHARD A. KRONMAL, PhD, and ANDRZEJ S. KOSINSKI, MSc

Estimates of the prevalence of atrial fibrillation (AF) in patients with coronary artery disease have varied from "frequent" to <2%. Data on 18,343 patients with angiographically demonstrated CAD in the Coronary Artery Surgery Study (CASS) registry were reviewed and AF was found to be present in 116 (0.6%) patients. The presence of AF was positively associated with the following clinical and angiographic variables: older age, sex (male), mitral regurgitation and functional impairment due to congestive heart failure. The number of diseased coronary arteries was negatively related to the presence of AF. Atrial fibrillation was an independent predictor of survival and its presence doubled the estimated risk over those patients without AF.

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Standard reference sources indicate that atrial fibrillation (AF) commonly occurs in patients with arteriosclerotic coronary artery disease (CAD).[1,2] The Framingham study[3] concluded that CAD is a "significant" precursor of chronic AF in men. Clinical[4] and angiographic[5,6] assessments of patients with proven CAD reveal an incidence of ≤2%. The pathophysiologic correlates of AF in chronic CAD are unclear. In a study of 1,126 patients with angiographic CAD, Kramer et al[6] found that in the 10 patients with AF this arrhythmia was related to left ventricular dysfunction and mitral regurgitation. In an analysis of 841 patients of varied etiologies, Haddad et al[5] wrote that, "in patients with severe left ventricular failure with multiple narrowings and low ejection fraction (10 to 25%) no AF was present." The present study evaluates the prevalence and significance of AF in the setting of angiographically proven CAD using the registry data of the Coronary Artery Surgery Study (CASS) (see Appendix).

From the Division of Cardiology, Department of Medicine, St. Luke's-Roosevelt Hospital Center and the College of Physicians and Surgeons, Columbia University, New York, New York, and the Departments of Biostatistics and Medicine, University of Washington, Seattle, Washington. The Coronary Artery Surgery Study (CASS) was funded by the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received June 6, 1987; revised manuscript received and accepted November 23, 1987.

Address for reprints: Airlie Cameron, MD, Division of Cardiology, St. Luke's-Roosevelt Hospital Center, Amsterdam Avenue and 114th Street, New York, New York 10025.

Methods

The CASS included a multicenter registry of all patients undergoing cardiac catheterization for suspected CAD.[7] From this registry, all patients with angiographic evidence of coronary artery stenosis ≥50% of luminal diameter were reviewed as to the presence of AF on the 12-lead baseline electrocardiogram. All electrocardiograms were read in a central electrocardiographic laboratory using criteria for interpretation derived from those developed by Blackburn et al.[8] The 116 patients with AF and CAD were compared with the 15,893 patients with sinus rhythm and CAD.

Definitions and calculation methods for all variables studied have been previously described in detail.[7] In addition to age and sex, other variables further described below were considered in the analysis. The presence of congestive heart failure and functional impairment were generally evaluated prior to cardiac catheterization. Congestive heart failure was considered present when the patient had clinical signs, symptoms or radiographic signs of congestion. The clinical symptoms and signs included orthopnea, paroxysmal nocturnal dyspnea, dyspnea on exertion, congestive hepatomegaly, ascites or peripheral edema. The radiographic signs included pleural fluid, pulmonary venous congestion and prominent pulmonary veins. Functional impairment due to congestive heart

failure was estimated as mild when symptoms occurred with heavy exercise, moderate when symptoms appeared with usual daily activities and severe when the patient was limited to bed-chair existence.

Cardiothoracic ratio was the ratio of the sum of the maximal half diameters of the heart from the midline and the maximal diameter of the chest at or above the upper level of the diaphragm. Left ventricular score was computed from wall motion evaluation of the left ventriculogram in the 30° right anterior oblique projection. As has been previously described,[7] a score of 5 indicated normal contractility whereas >10 was a sign of moderate impairment. The ejection fraction was calculated by the single-plane area-length method and the left ventricular end-diastolic pressure defined as the nadir following the atrial component of the left ventricular pressure pulse.

The number of arteries narrowed was defined as the number of major coronary arteries with lesions ≥70%. Two-vessel disease was diagnosed with ≥50% stenosis of the left main coronary artery. Mitral regurgitation was recorded as slight (minimal opacification), moderate (complete opacification over 3 to 4 cardiac cycles) and severe (complete opacification of the left atrium over 1 to 2 cardiac cycles). An aneurysm of the left ventricle was defined as a discrete area protruding from the expected outline of the ventricular chamber during systole. Patients with a history of previous treatment for hypertension were considered to have hypertension.

Follow-up was obtained with standardized questionnaries by mail and telephone for 8 years according to CASS protocol,[7] with 98% follow-up obtained.

The presence of AF was tabulated versus each of the aforementioned variables. Statistical testing of the independence of the arrhythmia status from a particular variable was performed via chi-square test. To determine the relation among all of the considered variables with AF status, a stepwise discriminant analysis was performed as an initial step to predict whether or not an individual will have AF on the basis of the various independent variables and this way to narrow down the number of variables of interest. Then a logistic regression, which serves a purpose similar to that of discriminant analysis but requires less restrictive assumptions, was performed on the smaller set of variables. The rationale for using discriminant analysis was to save computer time in screening the large number of variables considered.

The set of important predictive covariates was obtained along with their p values and estimated relative risks. All p values given are 2-sided. Relative risks for continuous variables are the risks associated with a 1-unit increase in a covariate value. Relative risks for categorical variables are the risks at particular levels of the covariate compared with the lowest level of that covariate.

A Cox regression analysis, useful in choosing important predictors of survival out of the set of variables, also was carried out. All variables were considered with the exception of ejection fraction and cardiothoracic ratio, for although both are statistically significantly predictors, they had many missing values and using them would considerably reduce the number of AF cases available for the analysis. Variables chosen as important predictors are reported together with p values and the instantaneous hazard ratios (referred to as relative risks). Interpretation of these relative risks is similar to that described for logistic regression. Survival curves were calculated by the lifetable method and compared by log-rank statistics.

Only p values <0.05 were considered statistically significant. All p values should be cautiously interpreted because of the large number of statistical tests carried out and the difficulty of verifying the assumptions underlying the multivariate procedures.

TABLE I Univariate Relation Between Age, Sex and Systemic Hypertension and the Presence of Atrial Fibrillation

	Sinus Rhythm (n = 15,893) No. (%)	AF (n = 116) No. (%)	p Value
Age 18–39	976 (6)	2 (2)	
40–59	10,703 (67)	52 (45)	<0.0001
≥60	4,214 (27)	62 (54)	
Men	13,253 (83)	107 (92)	0.0157
Hypertension	5,360 (34)	39 (34)	NS

AF = atrial fibrillation; NS = not significant.

Results

Atrial fibrillation was present in 116 (0.6%) of the 18,343 patients with angiographically demonstrated CAD in the CASS registry. Sinus rhythm was present in 15,893 (87%) patients. Other arrhythmias were premature beats (7%), sinus bradycardia (4.1%), sinus tachycardia (1.5%), ventricular or supraventricular tachycardias (0.08%), atrial flutter (0.07%), pacemaker (0.03%), wandering atrial pacemaker (0.01%)and atrial-ventricular dissociation (0.01%). The 116 patients with AF did not have any associated arrhythmia. Of

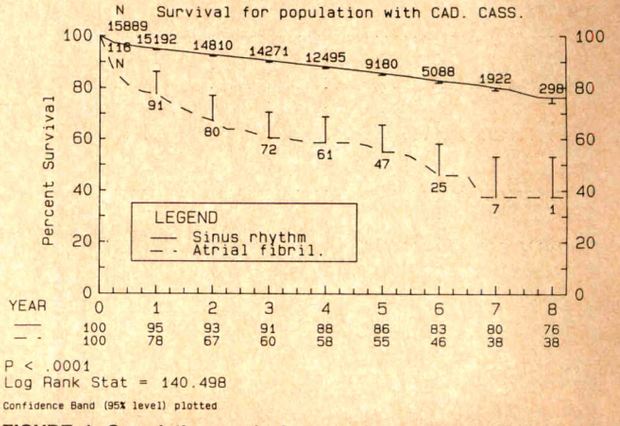

FIGURE 1. Cumulative survival curves for patients with coronary artery disease with and without atrial fibrillation. CAD = coronary artery disease; CASS = Coronary Artery Surgery Study.

TABLE II Univariate Relation Between Parameters of Ventricular Function and Presence of Atrial Fibrillation in Coronary Artery Disease

	Sinus Rhythm No. (%)	AF No. (%)	p Value
CHF present	1,713 (11)	58 (51)	<0.0001
Functional impairment			
0	243 (14)	4 (7)	
+	621 (36)	10 (17)	<0.0001
++	611 (36)	30 (52)	
+++	237 (14)	14 (24)	
CT ratio >0.55	485 (4)	17 (22)	<0.0001
LV score			
0–5	5,435 (35)	23 (21)	
6–10	5,818 (38)	32 (29)	<0.0001
>10	4,160 (27)	55 (50)	
Ejection fraction			
≤35%	1,071 (9)	28 (35)	<0.0001
36–50%	2,505 (21)	17 (22)	
>50%	8,241 (70)	34 (43)	
LVEDP (mm Hg)			
1–10	6,603 (42)	40 (35)	
11–20	6,825 (44)	55 (48)	0.0206
21–30	1,759 (11)	11 (10)	
>30	425 (3)	8 (7)	

AF = atrial fibrillation; CHF = congestive heart failure; CT = cardiothoracic; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; 0 = none; + = slight; ++ = moderate; +++ = severe.

TABLE III Influence of Features of Coronary Arteriogram and Ventriculogram on Prevalence of Atrial Fibrillation in Coronary Artery Disease

	Sinus Rhythm No. (%)	AF No. (%)	p Value
Major coronary arteries narrowed ≥70			
0	833 (5)	11 (9)	
1	4,332 (27)	27 (23)	0.0629
2	4,709 (30)	27 (23)	
3	6,019 (38)	51 (44)	
Segments narrowed			
1–2	4,482 (28)	34 (29)	
3–5	6,686 (42)	47 (41)	0.9417
6–8	3,583 (23)	28 (24)	
≥9	1,142 (7)	7 (6)	
Mitral regurgitation			
0	13,678 (88)	69 (61)	
+	1,576 (10)	23 (20)	<0.0001
++	275 (2)	15 (13)	
+++	52 (0)	7 (6)	
Left ventricular aneurysm	1,151 (7)	13 (12)	0.0865

AF = atrial fibrillation; 0 = none; + = slight; ++ = moderate; +++ = severe.

the 63 patients having repeat electrocardiograms during follow-up, 45 (71%) had sustained AF on 1 or more electrocardiograms, 3 had miscellaneous arrhythmias and 15 (24%) had reverted to sinus rhythm.

Atrial fibrillation in CAD was more common in patients older than 60 years of age ($p < 0.0001$) and in men ($p = 0.0157$) but was not influenced by history of hypertension (Table I). All parameters of ventricular function (Table II) showed a significant correlation of increasing impairment with a higher prevalence of AF. Neither the extent of CAD as measured by the number of segments diseased, nor the presence of a ventricular aneurysm affected the prevalence of AF (Table III); however, increasing severity of mitral regurgitation correlated with higher frequency of AF ($p < 0.0001$).

Using logistic regression analysis, the statistically significant independent predictors positively associated with atrial fibrillation were identified as age, sex, functional impairment and mitral regurgitation, all at $p < 0.0001$.

The relative risk associated with a 1-year increase in age was 1.07. Males were estimated to be at 5.4 times the risk of females. A comparison of patients with various degrees of functional impairment due to congestive heart failure with patients without congestive heart failure revealed a clear trend of greater relative risk with increasing impairment (relative risks of 2.48, 3.52, 8.15 and 6.03 for nonexistent, mild, moderate and severe impairment, respectively). Similarly, increasing severity of mitral regurgitation resulted in greater estimated relative risks when compared with patients without mitral regurgitation (relative risks of 1.91, 4.54 and 6.57 for slight, moderate and severe mitral regurgitation, respectively). The number of coronary arteries diseased was negatively associated with the presence of AF. The relative risk for patients with 1, 2, or 3 vessels was less than half (0.39, 0.28 and 0.27, respectively) that of patients with no arteries with >70% stenosis ("0-artery disease").

Atrial fibrillation, using Cox regression analysis, was an independent predictor of mortality with a relative risk of 1.982 (95% confidence interval 1.496, 2.626; $p < 0.0001$), as compared with sinus rhythm. Other predictors were high left ventricular score, functional impairment, moderate or severe mitral regurgitation, multiple CAD, history of hypertension and older age. The estimated probability of survival at 7 years (Figure 1) was 38% for patients with AF and 80% for patients in sinus rhythm ($p < 0.0001$).

Discussion

Observations as to the frequency of AF in CAD range from "common"[2] to 0.8% in 1,176 patients[6] or 0.2% in 496 patients.[5] The present study, carried out with a larger number of patients (18,343) and representing many hospitals and geographic areas, confirms a low overall frequency (0.6%) of AF in patients with angiographically proven CAD.

Previous studies[5,6] have disagreed as to the relation of AF to left ventricular dysfunction. The CASS data clearly established that AF is associated with the clinical features of congestive heart failure and the laboratory criteria reflective of left ventricular dysfunction or mitral regurgitation; however, it does not correlate with the extent of CAD as measured by the number of coronary artery segments with lesions of ≥50% stenosis. Atrial fibrillation is negatively associated with the number of major coronary arteries with ≥70% stenosis.

According to Ewy et al,[9] the causes of chronic AF include pathologic changes in the atrial wall, alter-

ations in the sinoauricular node and intranodal pathways, increasing age and left atrial pressure. In our study, the abnormal hemodynamics associated with left ventricular dysfunction and mitral regurgitation may have led to AF by increasing left atrial pressure and diameter. The increased incidence in males noted in our study and in previous reports[3,4] is not readily explained and may be related to some unknown variables such as alcohol consumption.[10]

Both paroxysmal and persistent AF are included in the present study. Because follow-up electrocardiograms were available in only 54% of patients presenting with AF, it was not possible to determine if the adverse effect of AF on survival was present in both the paroxysmal and persistent forms. Presumably, paroxysmal AF is a frequent percursor of persistent or sustained arrhythmia and would impart a similar adverse effect on survival. The prevalence of thromboembolic episodes was not investigated in this study but has been shown in other reports[11,12] to be greatly increased in patients with AF, particularly with associated mitral stenosis. The risk of systemic embolism in association with AF has been shown[12] to be almost as high in ischemic heart disease as with mitral valve disease. Undoubtedly, systemic embolism played a role in the impaired survival noted in this study of patients with AF.

The present study demonstrates that the presence of AF alone, without other stigmata of CAD, should prompt the physician to search for causes of AF other than angiographically demonstrated CAD.

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Appendix
Participating Institutions/Investigators

University of Alabama, Birmingham: William J. Rogers, MD,* Richard O. Russell, Jr., MD, Albert Oberman, MD, Nicholas T. Kouchoukos, MD. Albany Medical College: Julio A. Sosa, MD,* Martin F. McKneally, MD,* Joseph McIlduff, MD, Thomas Older, MD, Eric K. Foster, MD. Boston University: Thomas Ryan, MD,* David Faxon, MD, Laura Wexler, MD, Robert L. Berger, MD, Carolyn H. McCabe, BS. Loma Linda University: Melvin P. Judkins, MD,* Joan Coggin, MD.* Marshfield Medical Foundation, Inc. and Marshfield Clinic: William Myers, MD,* Richard D. Sautter, MD,* John N. Browell, MD, Dieter M. Voss, MD, Robert D. Carlson, MD. Massachusetts General Hospital: J. Warren Harthorne, MD,* W. Gerald Austen, MD,* Robert Dinsmore, MD, Frederick Levine, MD, John McDermott, MD. Mayo Clinic and Mayo Foundation: Robert L. Frye, MD,* Hugh C. Smith, MD, Ronald E. Vlietstra, MD, Michael B. Mock, MD, David R. Holmes, MD, Richard Fulton, MD. Miami Heart Institute: Arthur J. Gosseslin, MD,* Parry B. Larsen, MD, Paul Swaye, MD. Montreal Heart Institute: Martial G. Bourassa, MD,* Bernard R. Chaitman, MD, Claude Goulet, MD, Jacques Lesperance, MD. New York University: Ephraim Glassman, MD,* Michael Schloss, MD. St. Louis University: George Kaiser, MD,* J. Gerard Mudd, MD,* Robert D. Weins, MD, Hendrick B. Barner, MD, John E. Codd, MD, Denis H. Tyras, MD, Vallee L. Willman, MD. St. Luke's Hospital Center: Harvey G. Kemp, Jr., MD,* Airlie Cameron, MD. Stanford University: Edwin Alderman, MD,* Francis H. Koch, MD,* Paul R. Cipriano, MD,* James F. Silverman, MD,* Edward B. Stinson, MD.* Medical College of Wisconsin: Felix Tristani, MD,* Harold L. Brooks, MD,* Robert J. Flemma, MD. Yale University: Lawrence S. Cohen, MD,* Rene Langou, MD, Alexander S. Geha, MD, Graeme L. Hammon, MD, Richard K. Shaw, MD. Central Electrocardiographic Laboratory, University of Alabama: L. Thomas Sheffield, MD,* David Roitman, MD, Carol Troxell, BS. Coordinating Center, University of Washington: Lloyd Fisher, PhD,* Mary Jo Gillespie, MS, Kathryn Davis, PhD, J. Ward Kennedy MD, Richard Kronmal, PhD. Henry Ford Hospital: Thomas Killip, MD (Chairman of Steering Committee). National Heart, Lung, and Blood Institute: Eugene R. Pasamani, MD, Peter L. Frommer, MD, Suzanne M. Mullin, RN, MPH, Kent Bailey, PhD, David DeMets, PhD.

*Principal investigator.

Helicopter Transport of Patients During Acute Myocardial Infarction

RAYE L. BELLINGER, MD, ROBERT M. CALIFF, MD, DANIEL B. MARK, MD, MPH, RITA A. WEBER, RN, MS, PATRICIA COLLINS, RN, JANICE STONE, RN, HARRY R. PHILLIPS, III, MD, LAWRENCE GERMAN, MD, and RICHARD S. STACK, MD

Initial experience with a regional system of emergency helicopter transport of patients with acute myocardial infarction (AMI) referred for emergent cardiac catheterization and percutaneous transluminal coronary angioplasty (PTCA) is described. Two hundred fifty patients with AMI were transported from within a 150-mile radius to Duke University Medical Center over a 15-month period. All patients were within 12 hours of onset of symptoms. Thrombolytic therapy was administered to 240 (96%) patients (72% before or in-flight). The time to administration of thrombolytic therapy ranged from 30 to 120 minutes (median 180), while the time to arrival in the interventional catheterization laboratory ranged from 105 to 815 minutes (median 300). The flight time was 12 to 77 minutes (median 31). Most patients had 1- or 2-vessel coronary artery disease; the baseline ejection fraction ranged from 27 to 70% (median 42). Transient hypotension was the most common complication both pre-flight and in-flight. Third-degree atrioventricular block and nonsustained ventricular tachycardia were the next most common complications. Ventricular fibrillation or sustained ventricular tachycardia occurred before takeoff in 38 patients (15%). No patients had ventricular fibrillation, asystole or respiratory arrest during transport. Fluid boluses for hypotension were the most common intervention. Five patients required cardiopulmonary resuscitation in-flight; 3 before liftoff and 2 required a brief period of cardiopulmonary resuscitation during sustained ventricular tachycardia. Fourteen patients had pressor therapy, military antishock trousers or both to maintain adequate blood pressure. Neither cardioversion, defibrillation nor intubation were performed in-flight. Thus, in-flight complications are infrequent and can be managed en route to an intervention center. The overall benefit of regional helicopter transportation relative to its cost has yet to be determined.

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Address for reprints: Robert M. Califf, MD, Division of Cardiology, Department of Medicine, P.O. Box 31123, Duke University Medical Center, Durham, NC 27710.

Therapies designed to achieve early and sustained coronary reperfusion in patients with acute myocardial infarction (AMI) decrease in-hospital mortality[1] and improve left ventricular function[2,3] compared with standard therapy. Intravenous thrombolytic therapy alone has 2 major shortcomings. First, a significant number of patients fail to achieve reperfusion. Second, a significant atherosclerotic plaque often remains after successful thrombolytic therapy, increasing the risk of recurrent infarction[4] and periinfarction ischemia.[5] Percutaneous transluminal coronary angioplasty (PTCA) provides a reasonable adjunct to thrombolytic therapy because it often achieves reperfusion where thrombolysis fails[6] and it increases the luminal diameter narrowed by the residual atherosclerotic plaque.[7]

An interventional program including thrombolytic therapy, acute cardiac catheterization, PTCA and coronary artery bypass surgery is beyond the means of many hospitals. However, patients admitted to such institutions may benefit from a regional system that includes immediate thrombolysis followed by rapid transportation of patients with AMI to a nearby intervention center. While a helicopter is the most efficient means of transportation for distances up to 150 miles, concerns have arisen about the safety of such transportation for potentially unstable AMI patients. This study examines our initial experience with a regional system of helicopter transport of patients in the early stages of AMI with particular attention to the complications encountered.

Methods

The Duke LifeFlight Helicopter Service began transporting critically ill patients in March 1985. Many patients were transported for interventional cardiac catheterization during AMI. Because of established referral patterns with community hospitals and the limited range of the helicopters used, most flights stayed within a 150-mile radius of our medical center.

Patients were considered to have an AMI if they met the following criteria: (1) a compatible clinical history of chest pain or equivalent of <12 hours in duration; (2) at least 1 mm of ST elevation in at least 2 of 6 anterior leads (V_1 through V_6), 2 of 3 inferior leads (II,III, aVF) or both lateral leads (I, aVL); (3) no resolution of ST elevation with 0.4 mg sublingual nitroglycerin in 3 consecutive doses. Once patients fulfilled the criteria for AMI, thrombolytic therapy was usually administered after intravenous premedication with 50 mg diphenhydramine and 300 mg cimetidine. Patients who were at high risk of bleeding or had other known contraindications to thrombolytic therapy did not receive thrombolytic agents.

Streptokinase was the predominant thrombolytic agent used; 1.5 million units of streptokinase mixed in 250 cc of 5% dextrose and water was infused intravenously over a 30- to 45-minute period. During the course of this study, recombinant tissue-type plasminogen activator was made available to patients with the entry requirements of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial. The study protocol and dosing regimen for the recombinant tissue-type plasminogen activator infusion have been described previously.[8]

Patients were designated as meeting the criteria for AMI by their referring physicians. The referring physicians then notified either the Duke cardiologist on-call or the Duke LifeFlight medical control officer on-call to arrange transfer of the patient. A helicopter and flight crew consisting of an experienced pilot and 2 flight nurses with previous critical care experience were dispatched to the referring hospital. If the weather conditions were adverse (20% of flight requests), alternative transport by ambulance was arranged or the patient was not transferred. At the discretion of the referring physician and the Duke accepting physician, thrombolytic therapy was started either at the community hospital, during air transport or at Duke University Medical Center. Vasoactive, antiarrhythmic and other specialized therapy was initiated by the referring physician as needed. After acceptance of the patient, the flight crew radioed the patient's status to the Duke medical control officer and, during the transport, notified the medical control officer of any changes in the patient's status so that existing therapy could be modified or new therapy initiated. Changes in patient status and interventions were documented by the flight team.

Upon arrival at Duke, all patients underwent diagnostic cardiac catheterization and, when clinically indicated, coronary angioplasty or coronary artery bypass grafting. Each patient's flight record and in-patient chart were reviewed to ascertain complications and interventions during transport and throughout the hospitalization.

TABLE I Patient Data: Quartiles

	25%	Median (50%)	75%
Age (yr)	47	58	63
Time to thrombolytic therapy (min)*	130	185	280
Time to catheterization (min)†	240	304	403

* Time from the onset of chest pain to the start of thrombolytic therapy.
† Time from the onset of chest pain to the start of cardiac catheterization.

Results

From March 1, 1985, through June 30, 1986, 1,597 critically ill patients were transported from community hospitals to Duke University Medical Center. Within the group transported for cardiac reasons (n = 896), 250 patients met the study criteria for AMI. Most patients (96%) were given thrombolytic therapy: intravenous streptokinase was administered to 77%; intravenous recombinant tissue plasminogen activator was administered to 19%; and 4% (10/250) of patients did not receive thrombolytic therapy because of contraindications. Thrombolytic therapy was started at the referral hospital in 70% (168/240), in-flight in 5% (12/240) and at Duke University Medical Center in 25% (60/240) of patients.

Tables I and II summarize the clinical and transport-related variables. Thrombolytic therapy was started early in most patients (median of 3 hours from symptom onset) and cardiac catheterization was performed within 2 hours of thrombolytic therapy treatment in most patients.

All patients underwent emergency coronary arteriography and ventriculography upon arrival at Duke. Only 3 (1%) patients were found to have insignificant coronary artery disease (i.e., ≤50% diameter stenosis in all major coronary vessels). One hundred and seven (43%) patients had 1-vessel coronary artery disease, 93

TABLE II Transport Data: Quartiles

	25%	Median (50%)	75%
Distance by air (miles)*	40	61	98
Time from call to arrival (min)†	95	138	172
Time in air (min)‡	21	31	50
Estimated ground distance (miles)	57	81	109

* Distance by air from Duke Hospital to community hospitals.
† Time from a call received by the LifeFlight dispatcher until the patient arrived at Duke Hospital.
‡ Time required to transport patient from community hospital to Duke University Medical Center by air.

TABLE III Complications During Helicopter Transport of Patients with Acute Myocardial Infarction

	Pre-Flight (n)	In-Flight (n)	Total (n)
Sinus bradycardia (HR <40 beats/min)	10	4	14
Atrial fibrillation/flutter	3	3	6
Ventricular fibrillation	19	0	19
Ventricular tachycardia sustained	19	3	22
Ventricular tachycardia nonsustained	6	7	13
Asystole	1	0	1
Third-degree AV block	19	8	27
Second-degree AV block type I	2	0	2
Second-degree AV block type II	3	0	3
Transient hypotension*	30	21	51
Sustained hypotension†	20	4	24
Respiratory arrest	9	0	9

* Defined as a systolic blood pressure of <90 mm Hg for <1 hour.
† Defined as a systolic blood pressure of <90 mm Hg for >1 hour.
AV = atrioventricular; HR = heart rate.

(37%) had 2-vessel disease and 48 (19%) had 3-vessel disease. The baseline ejection fraction was 42%. Five percent of patients had coexistent left main disease.

One hundred and eighty-eight (75%) patients underwent PTCA during their admission; 176 (94%) were performed emergently (i.e., at the time of the cardiac catheterization). Persistent reperfusion (i.e., sustained angiographic perfusion of the infarct-related artery) was obtained in 94% of the patients who underwent emergent coronary angioplasty. Forty-five (18%) patients underwent coronary artery bypass grafting during admission for either severe 3-vessel disease, coexistent left main disease or failed reperfusion by PTCA. Seventeen (7%) patients were reperfused with thrombolytic therapy alone and, because of no significant residual coronary stenosis in the infarct-related artery after thrombolysis, did not undergo either coronary angioplasty or coronary artery bypass grafting.

Table III summarizes the pre-flight and in-flight complications encountered during the transport of patients with AMI. Transient hypotension (systolic blood pressure of <90 mm Hg for <1 hour) was the most frequent complication both pre-flight and in-flight. Third-degree atrioventricular block was the second most frequent in-flight complication followed by nonsustained ventricular tachycardia. Sustained ventricular tachycardia was only encountered in 3 patients. No patient had ventricular fibrillation, asystole or respiratory arrest while in-flight; yet 19 patients had ventricular fibrillation and 19 patients had sustained ventricular tachycardia before air transport.

Table IV lists therapeutic interventions made by the LifeFlight medical crew both pre-flight and in-flight for these patients. Fluid boluses for transient and sustained hypotension were the most frequent therapy during air transport. Fourteen patients required either pressor therapy, use of military antishock trousers or both to maintain adequate blood pressure. Thirty-four patients required cardiopulmonary resuscitation pre-flight. Five patients received cardiopulmonary resuscitation during air transport: 3 had been receiving cardiopulmonary resuscitation pre-flight with continuation during transport, and 2 patients with sustained ventricular tachycardia required cardiopulmonary resuscitation for a short time before spontaneously converting to sinus rhythm. Cardioversion, defibrillation or intubation was not necessary during any of the air transports.

The majority of patients received lidocaine before transport as prophylactic antiarrhythmic therapy. All patients who received antiarrhythmic therapy while in-flight did so because of ventricular or supraventricular arrhythmias that were felt to be life-threatening. Hemodynamically unstable bradyarrhythmias in the form of severe sinus bradycardia (heart rate <40 beats/min) and third-degree atrioventricular block were generally treated initially with atropine. In 3 patients, an external pacemaker had been placed pre-flight and was used in-flight. Fifteen patients with temporary transvenous pacemakers placed pre-flight were transported without incident.

Emergency landing: On July 21, 1986, while transporting a patient from a referring hospital to Duke, the helicopter experienced a power loss at an altitude of 2,500 feet. The aircraft was transporting a 62-year-old man with an anterior AMI. He had been given 1.5 million units of streptokinase just before takeoff. The pilot successfully landed the aircraft in an open field. The pilot, crew and patient suffered only minor injuries, but the aircraft was damaged beyond repair. The patient was subsequently transported to Duke University Medical Center by a second helicopter and arrived at Duke approximately 90 minutes after the emergency landing.

Discussion

The most important finding of our study is the relatively small number of complications encountered by our patients while they were being transported from

their community hospitals. The low complication rate is especially remarkable in view of the large number of complications they experienced before transfer. Patients who suffered complications before transport may, in fact, have benefitted more from helicopter transfer than other patients because of the greater risk that a long ground trip to a tertiary center poses to an unstable patient.

The rarity of both ventricular tachycardia and fibrillation during flight may have resulted from the frequent use of antidysrhythmic prophylaxis before takeoff. Nonsustained ventricular tachycardia was treated with a bolus infusion of either lidocaine or procainamide; patients who did not respond were given bretylium. All 3 patients developing sustained ventricular tachycardia in-flight spontaneously converted to sinus rhythm prior to direct current countershock. Two of the 3 patients received brief cardiopulmonary resuscitation by 1 crewmember while the other crewmember was preparing to administer a direct current countershock. All 3 patients had received lidocaine therapy before liftoff.

Patients who developed severe bradyarrhythmias (severe sinus bradycardia or high grade second- or third-degree atrioventricular block) were first treated with atropine. If a transcutaneous external pacemaker was available, the patient was paced externally as needed; in the absence of an external pacemaker, or if the patient did not respond to atropine, isoproterenol was infused. None of the 3 patients developing atrial fibrillation or flutter required therapy during transport.

The helicopter transport system used in this study has certain advantages over conventional ambulance transport. The care given in the helicopter by 2 highly-trained critical care nurses in constant radio communication with a physician at the tertiary center is likely to be more effective than care rendered in an ambulance. Even when a physician accompanies a patient during ground transport, the environment lacks the physical stability possible within a helicopter, which allows for careful monitoring and control of blood pressure, cardiac rhythm and therapeutic infusions. When specific interventions, such as volume, antidysrhythmic and inotropic infusions are required, the medical flight team can maintain precise control with physician guidance by radio communication.

While the total amount of time from referral to arrival at the tertiary center may not be less with helicopter transport, the amount of time the patient spends travelling between hospitals is markedly diminished. The patient remains under the careful management of the referring physician until the arrival of the helicopter, minimizing the time in a less controlled environment. This aspect of helicopter transport also preserves local emergency medical transport resources, making it unnecessary for a physician or nurse from the community hospital to accompany the patient to the tertiary hospital, as is frequently the case with ambulance transport. The loss of medical personnel and equipment, especially in smaller communities, impairs the ability of the local medical services to respond to other emergencies. Helicopter transport with constant radio communication also makes it possible for the tertiary center to prepare for the patient being transported, based on information passed between helicopter and hospital about the status of the patient. Many of the potential advantages of this system pertain more to the personnel and equipment for communication than to the specific mode of transport. A similar system could be developed for specialized ambulance and fixed-wing transport.

TABLE IV Interventions During Helicopter Transport of Patients with Acute Myocardial Infarction

	Pre-Flight (n)	In-Flight (n)	Total (n)
CPR	34	5	39
Cardioversion/defibrillation	24	0	24
Intubation	12	0	12
Fluid bolus	29	24	53
MAST	0	7	7
External pacer	3	3	6
Transvenous pacer	15	0	15
Atropine	13	7	20
Isoproterenol	3	2	5
Lidocaine	196	10	206
Procainamide	6	0	6
Bretylium	7	2	9
Dopamine	30	5	35
Dobutamine	6	0	6
Levophed	0	2	2

CPR = cardiopulmonary resuscitation; MAST = military antishock trousers.

Aircraft safety is an important and controversial issue, which has major ramifications for the transport of critically ill patients. From 1980 to 1986, there have been 66 aeromedical helicopter crashes; 21 people have died and 16 have been injured. At present, there are approximately 171 aeromedical helicopter services operating throughout the U.S. For 1986, the accident rate for medical helicopters was 17.7/100,000 patient transports.[9] Documented causes of these crashes include catastrophic mechanical failures and pilot error during operation in marginal weather conditions. Recently, the American Society of Hospital-Based Air Medical Services has published guidelines concerning pilot and crew standards, aircraft operating and equipment and maintenance standards in order to improve safety during aeromedical transports.[10] Details of our safety standards have been published elsewhere.[11]

Intravenous thrombolytic therapy is the most common technique used in clinical practice today for rapid reperfusion of infarct-related vessels. It is especially suited to community hospitals, which may not have the resources to support a full-time interventional cardiac catheterization facility capable of acute coronary angioplasty and emergency coronary bypass surgery. Intravenous thrombolytic therapy has a reperfusion rate of 30 to 70% in well-controlled trials. For the 30 to 70% of patients who do not respond to thrombolytic therapy in a community hospital without interventional facili-

ties, transportation of the patient to a specialized interventional center will improve the chances of infarct-vessel patency.

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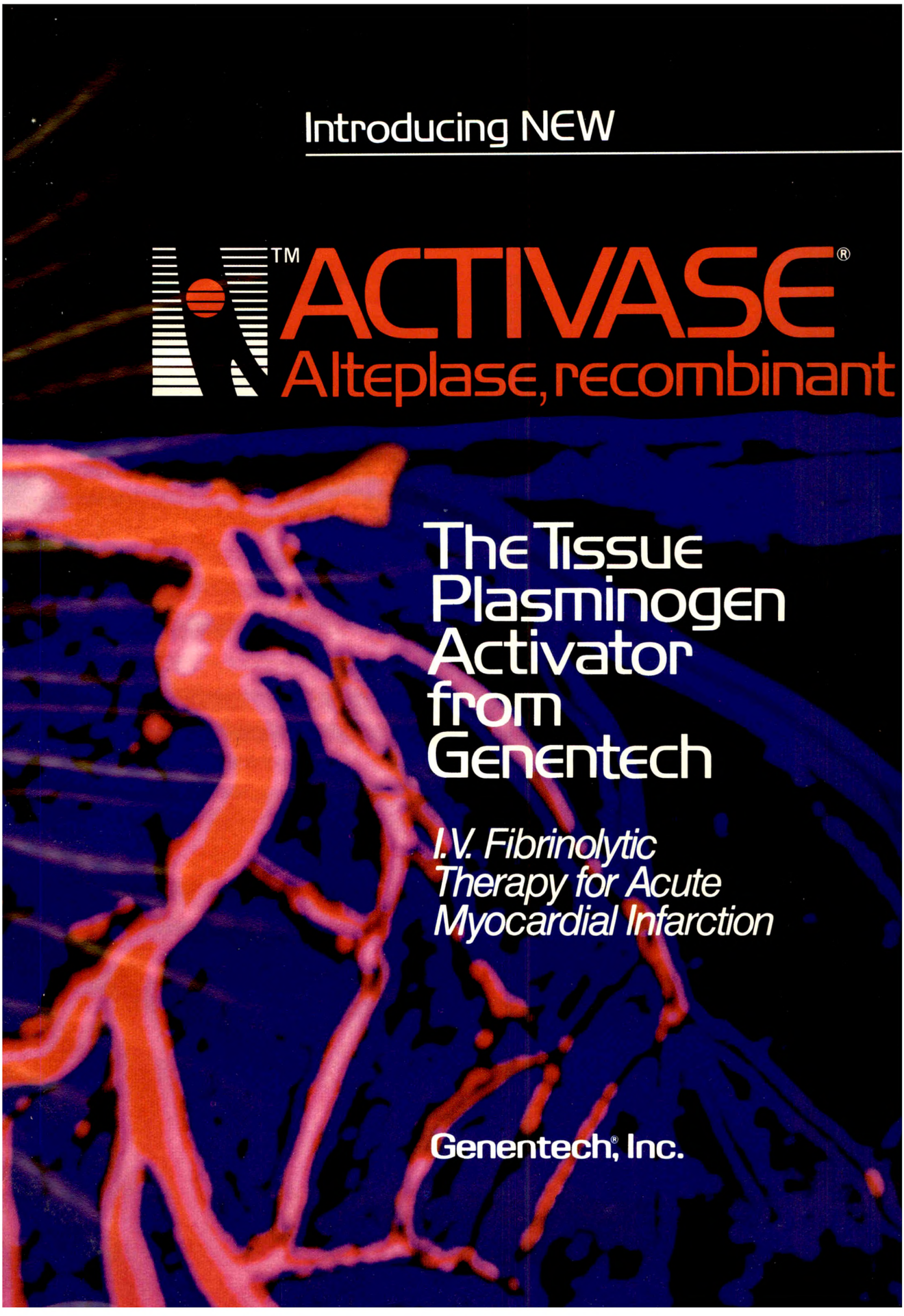

Introducing NEW
rt™ ACTIVASE®
Alteplase, recombinant
The Tissue Plasminogen Activator from Genentech
I.V. Fibrinolytic Therapy for Acute Myocardial Infarction
Genentech, Inc.

NEW

ACTIVASE®

Alteplase, recombinant

A tissue plasminogen activator

The biopharmaceutical equivalent of the body's own natural

t-PA

IN ACUTE MYOCARDIAL INFARCTION,

TIME IS MUSCLE

...Rapid dissolution of occlusive coronary thrombi

...High rate of recanalization

...Preservation of ventricular function

...Excellent safety profile

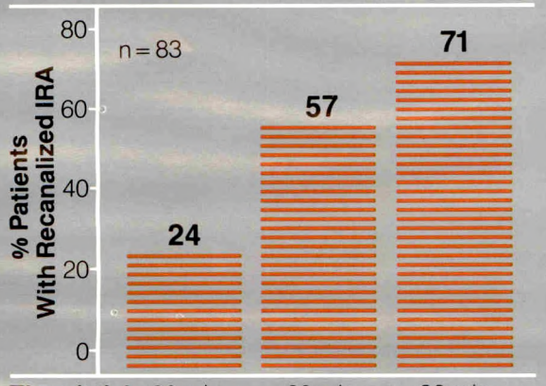
FIBRINOLYTIC EFFICACY

ACTIVASE® OPENS CORONARY ARTERIES

Fast

▲ The Average Time to Successful Recanalization is Between 30 and 60 Minutes.[1]

RECANALIZATION RATE FOLLOWING ACTIVASE® THERAPY 100 MG/3 HRS

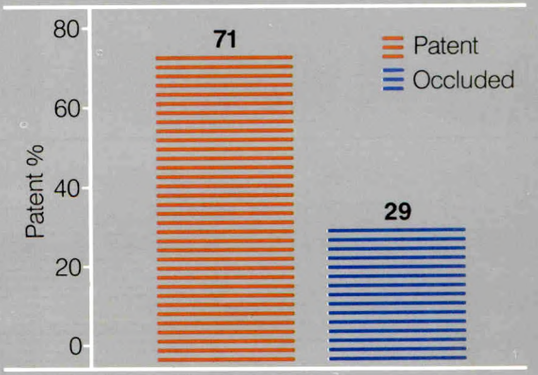


Time (min)	30 min	60 min	90 min
Cumulative Dose (mg)	33	60	70

Effectively

▲ 71% Recanalization Demonstrated in Acute MI Patients[1]

RECANALIZATION RATE 90 MINUTES AFTER ACTIVASE® THERAPY NIH-TIMI B TRIAL



...And Keeps Them Open

Low Reocclusion Rate:

▲ Pooled incidence of reocclusion was less than 13% after ACTIVASE® administration.[2]

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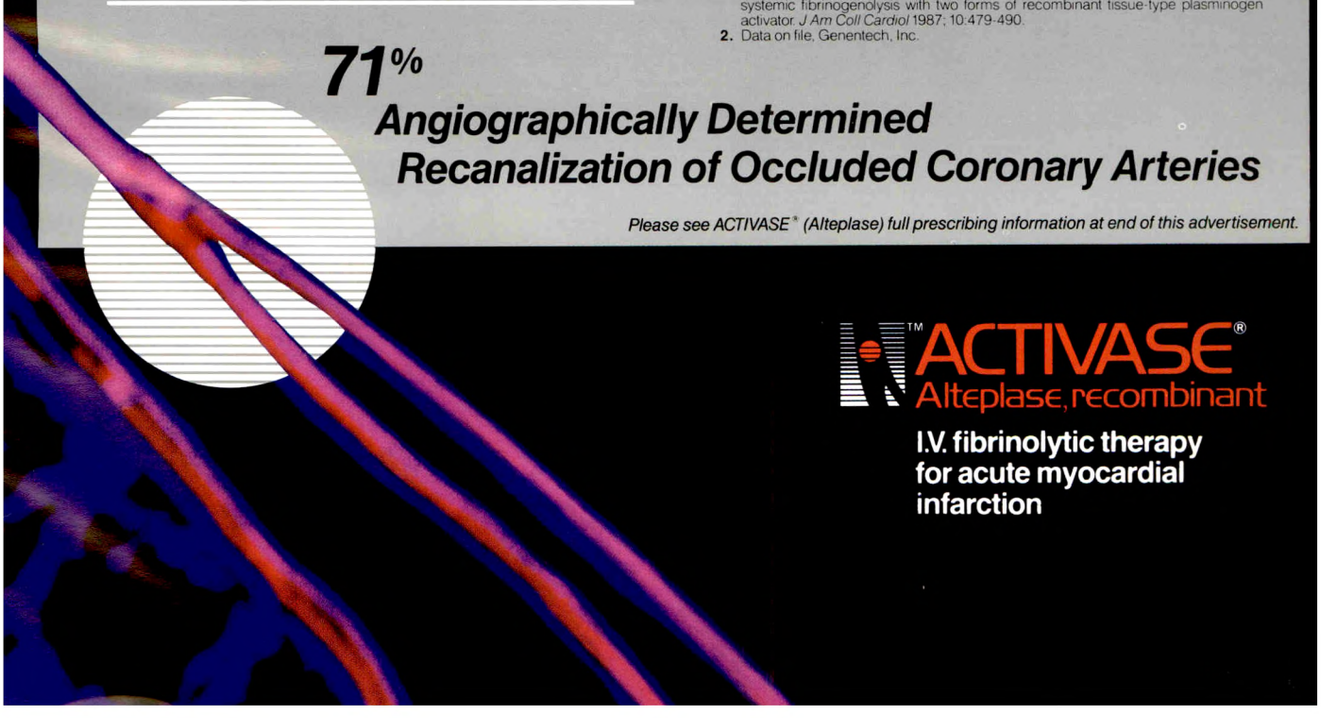
2. Data on file, Genentech, Inc.

71%

Angiographically Determined Recanalization of Occluded Coronary Arteries

Please see ACTIVASE® (Alteplase) full prescribing information at end of this advertisement.



ACTIVASE®
Alteplase, recombinant

I.V. fibrinolytic therapy for acute myocardial infarction

NEW

ACTIVASE®
Alteplase, recombinant

MYOCARDIAL SALVAGE

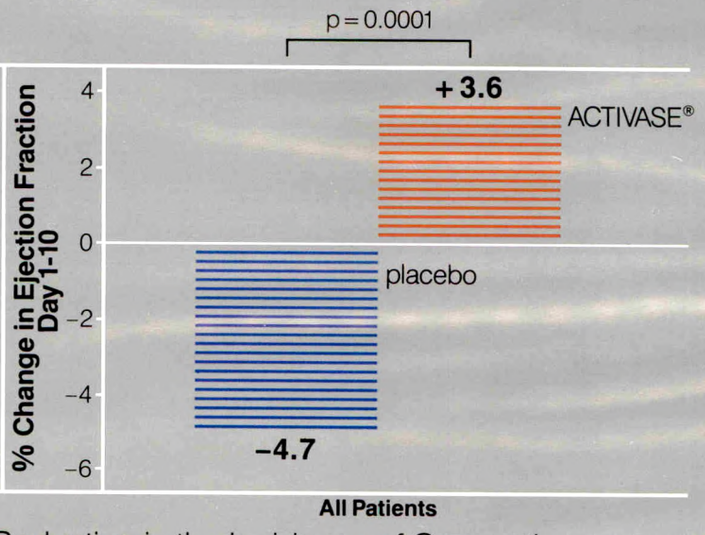
ACTIVASE® IMPROVES LEFT VENTRICULAR FUNCTION

▲ Significant Difference in Ejection Fraction Between Placebo and ACTIVASE®-Treated Patients[3]

Well-controlled studies document significant preservation of ventricular function:

1. The JOHNS HOPKINS Study

At day 10 after acute myocardial infarction, patients treated with ACTIVASE® had a statistically significant recovery of ejection fraction, while placebo patients had a further deterioration from baseline.



▲ In Addition, There Was a 58% Reduction in the Incidence of Congestive Heart Failure Following MI in the ACTIVASE®-Treated Group. (p = 0.009)[3]

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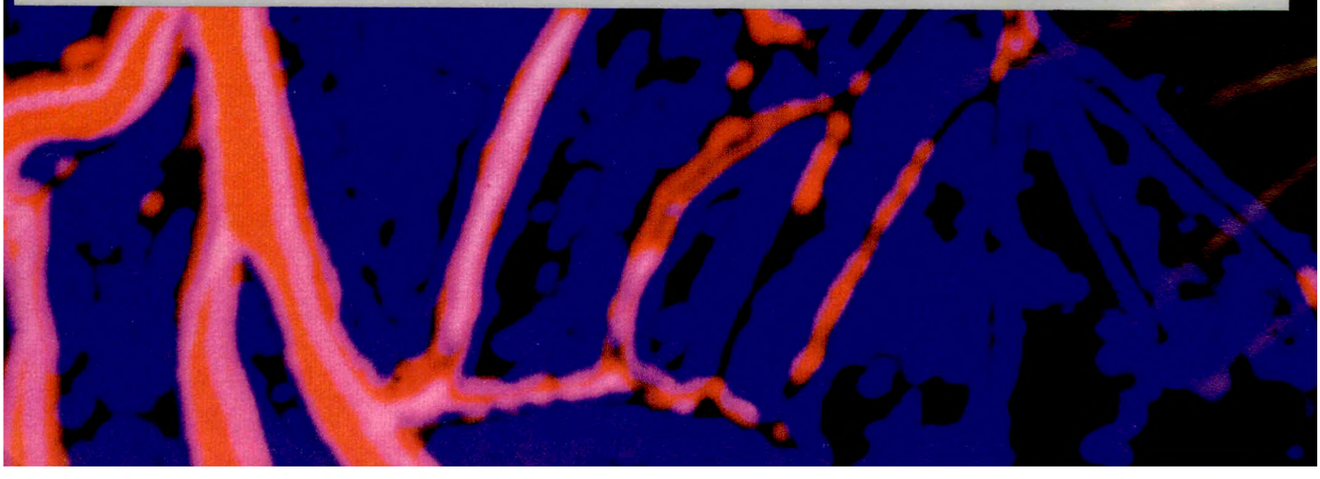


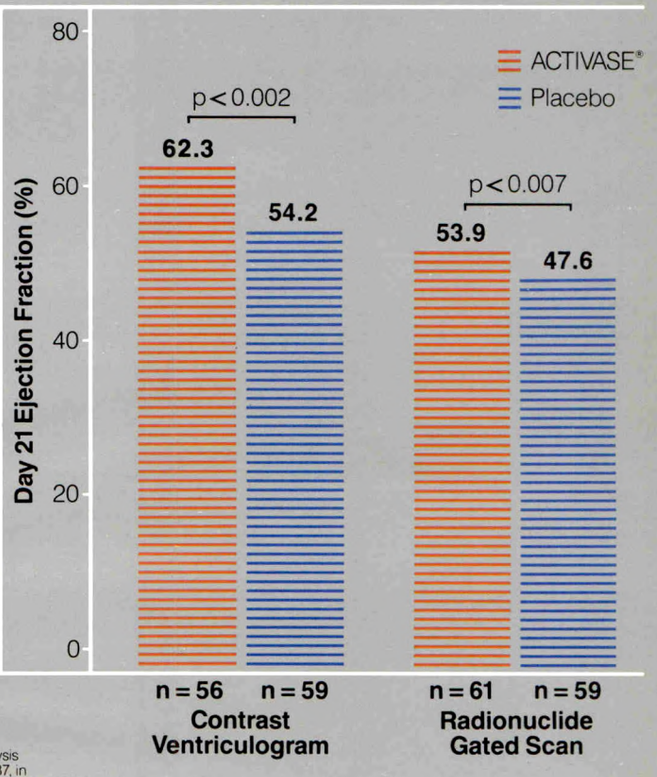
In Acute Myocardial Infarction,

TIME IS MUSCLE

2. The TICO Trial[4] *(THROMBOLYSIS IN CORONARY OCCLUSION)*

Following acute MI, and administration of ACTIVASE® or placebo, contrast ventriculogram and radionuclide gated scans were performed.

Results showed that ACTIVASE®-treated patients had significantly greater residual left ventricular ejection fractions at discharge.



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Please see ACTIVASE® (Alteplase) full prescribing information at end of this advertisement.

ACTIVASE®
Alteplase, recombinant

I.V. fibrinolytic therapy for acute myocardial infarction

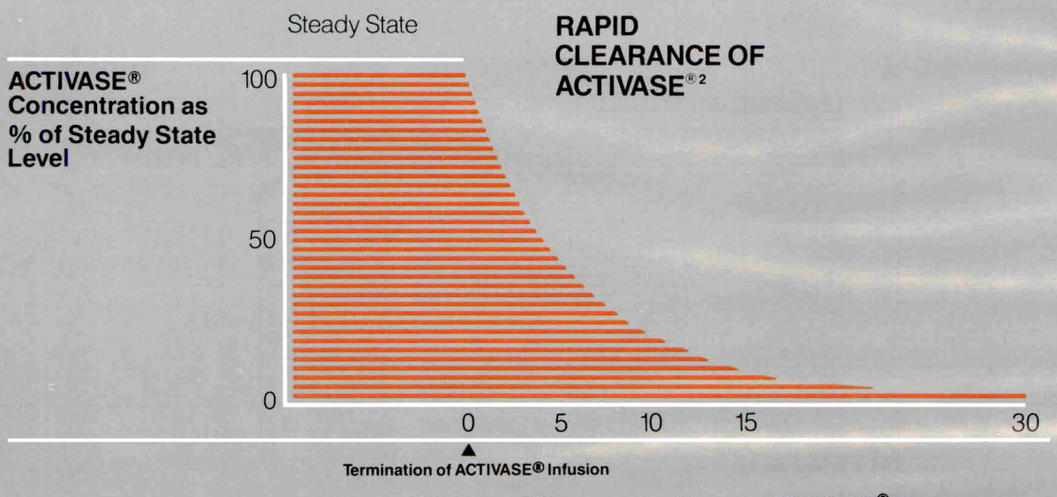
NEW

ACTIVASE®
Alteplase, recombinant

FIBRINOLYTIC SAFETY

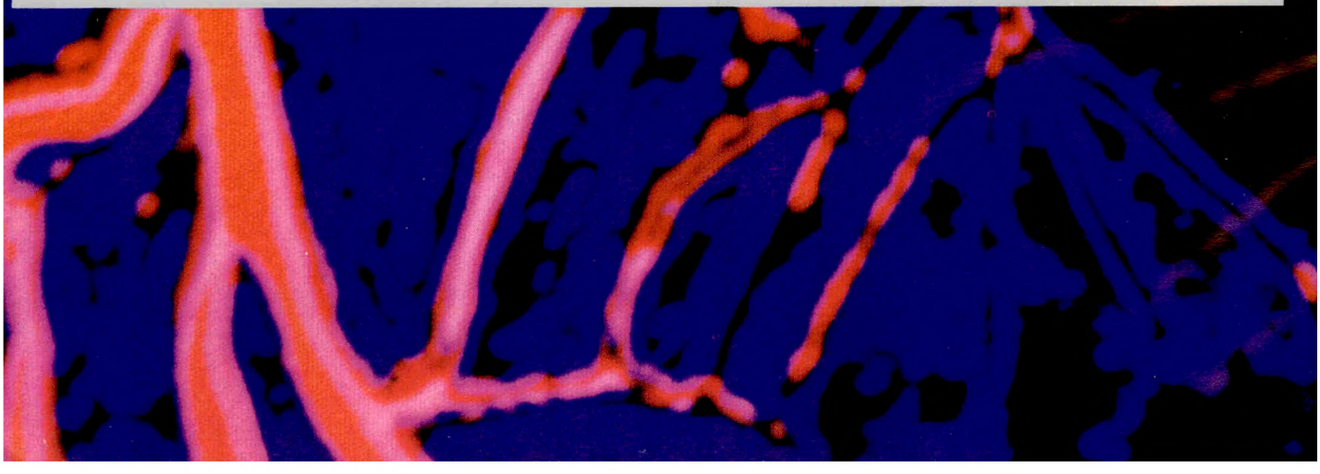
EXCELLENT SAFETY PROFILE IN ACUTE MI:

▲ FIVE-MINUTE HALF-LIFE AND FIBRIN SPECIFICITY Lower the Risk of Serious Bleeding in Emergency Procedures Such as Hemodynamic Monitoring, Angioplasty and Bypass Surgery (CABG).



▲ ACTIVASE® Is Identical to Human Tissue Plasminogen Activator (t-PA). No Serious or Life-Threatening Reactions Have Been Reported.

2. Data on file, Genentech, Inc.



In Acute Myocardial Infarction,

TIME IS MUSCLE

Bleeding is the Most Common Complication of Thrombolytic Therapy

INCIDENCE OF BLEEDING COMPLICATIONS FOLLOWING ACTIVASE® IN 848 PATIENTS:

Bleeding site	Clinically significant events %
–Arterial catheterization site	20
–Gastrointestinal (GI)	5
–Venipuncture	4
–Hematuria	4
–Occult GI	1
–Microscopic hematuria	1
–Ecchymosis	1
–Retroperitoneal	< 1
–Intracranial	0.4

Careful Patient Selection Can Optimize the Benefit-to-Risk Ratio. Consider These Factors in Evaluating an Individual for ACTIVASE® Therapy:

CONTRAINDICATIONS

–Active internal bleeding
–History of cerebrovascular accident
–Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS)
–Intracranial neoplasm, arteriovenous malformation, or aneurysm
–Known bleeding diathesis
–Severe uncontrolled hypertension

Please see ACTIVASE® (Alteplase) full prescribing information at end of this advertisement.

ACTIVASE®
Alteplase, recombinant

I.V. fibrinolytic therapy for acute myocardial infarction

NEW

ACTIVASE®
Alteplase, recombinant

In Acute Myocardial Infarction,
TIME IS MUSCLE

Rationale for ACTIVASE® Therapy

Acute MI is an evolving process caused by an occlusive coronary thrombus

I.V. administration of ACTIVASE®:

- *Opens coronary arteries rapidly, effectively, and keeps them open*
- *Improves left ventricular function, and reduces incidence of congestive heart failure*
- *Prompt intervention possible shortly after ACTIVASE® therapy due to excellent safety profile—compatible with angioplasty, bypass surgery and hemodynamic monitoring*

ACTIVASE® is a potent agent, and the benefit-to-risk ratio should be carefully considered in every patient

ACTIVASE® Dosage Schedule

Lytic dose	Bolus Hr 1	6-10mg 50-54mg
Maintenance Dose	Hr 2 Hr 3	20mg 20mg
TOTAL Recommended Dose		100mg

Available from GENENTECH

- ACTIVASE® Dosage Chart
- ACTIVASE® Product Monograph

For further information, answers to medical inquiries, and requests for literature, call the GENENTECH INFARCT LINE

1-800-821-8590

Genentech®, Inc.
460 Point San Bruno Blvd.
South San Francisco, CA 94080

Please see ACTIVASE® (Alteplase) full prescribing information at end of this advertisement.

ACTIVASE®
Alteplase, recombinant

I.V. fibrinolytic therapy for acute myocardial infarction

ACTIVASE®
Alteplase, recombinant

DESCRIPTION: ACTIVASE®, Alteplase, is a tissue plasminogen activator produced by recombinant DNA technology. It is a sterile, purified glycoprotein of 527 amino acids. It is synthesized using the complementary DNA (cDNA) for natural human tissue-type plasminogen activator obtained from a human melanoma cell line. The manufacturing process involves the secretion of the enzyme, alteplase, into the culture medium by an established mammalian cell line (Chinese Hamster Ovary cells) into which the cDNA for alteplase has been genetically inserted.

ACTIVASE®, a sterile, white to off-white, lyophilized powder, is intended for intravenous administration after reconstitution with Sterile Water for Injection, USP. The quantitative composition of the lyophilized product is:

50 mg (29 million IU) Vial	20 mg (11.6 million IU) Vial
Alteplase 50 mg (29 million IU)	Alteplase 20 mg (11.6 million IU)
L-Arginine 1.7 g	L-Arginine 0.7 g
Phosphoric Acid 0.5 g	Phosphoric Acid 0.2 g
Polysorbate 80, less than 4 mg	Polysorbate 80, less than 1.6 mg

Phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment.

Biological potency is determined by an *in vitro* clot lysis assay and is expressed in International Units as tested against the WHO standard. The specific activity of ACTIVASE® is 580,000 IU/mg.

CLINICAL PHARMACOLOGY: ACTIVASE® is an enzyme (serine protease) which has the property of fibrin-enhanced conversion of plasminogen to plasmin. It produces limited conversion of plasminogen in the absence of fibrin. When introduced into the systemic circulation at pharmacologic concentration, ACTIVASE® binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin. This initiates local fibrinolysis with limited systemic proteolysis. Following administration of 100 mg ACTIVASE®, there is a decrease (16-36%) in circulating fibrinogen.[1,2,3] In a controlled trial, 8 of 73 patients (11%) receiving ACTIVASE® (1.25 mg/kg body weight over 3 hours) experienced a decrease in fibrinogen to below 100 mg/dL.[2]

ACTIVASE® is cleared rapidly from circulating plasma at a rate of 550-680 mL/min. ACTIVASE® is cleared primarily by the liver. More than 50% of ACTIVASE® present in plasma is cleared within 5 minutes after the infusion has been terminated, and approximately 80% is cleared within 10 minutes.

Coronary occlusion due to a thrombus is present in the infarct-related coronary artery in approximately 80% of patients experiencing a transmural myocardial infarction evaluated within four hours of onset of symptoms.[4,5]

In patients studied in a controlled trial with coronary angiography at 90 and 120 minutes following infusion of ACTIVASE®, infarct artery patency was observed in 71% and 85% of patients (n=85), respectively.[2,3] In a second study, where patients received coronary angiography prior to and following infusion of ACTIVASE® within six hours of the onset of symptoms, reperfusion of the obstructed vessel occurred within 90 minutes after the commencement of therapy in 71% of 83 patients.[1]

In a double blind, randomized trial (138 patients) comparing ACTIVASE® to placebo, patients infused with ACTIVASE® within 4 hours of onset of symptoms experienced improved left ventricular function at day 10 compared to the placebo group, when ejection fraction was measured by gated blood pool scan (53.2% versus 46.4%, p=0.018). Relative to baseline (day 1) values, the net changes in ejection fraction were +3.6% and -4.7% for the treated and placebo group, respectively (p=0.0001). Also documented was a reduced incidence of clinical congestive heart failure in the treated group (14%) compared to the placebo group (33%) (p=0.009).[3]

In a second double blind, randomized trial (136 patients) comparing ACTIVASE®, Alteplase, to placebo, patients infused with ACTIVASE® within 2.5 hours of onset of symptoms experienced improved left ventricular function at a mean of 21 days compared to the placebo group, when ejection fraction was measured by gated blood pool scan (54% versus 48%, p=0.008) and by contrast ventriculogram (62% versus 54%, p=0.002). Although the contribution of ACTIVASE® alone is unclear, the incidence of nonischemic cardiac complications when taken as a group (i.e., congestive heart failure, pericarditis, atrial fibrillation, conduction disturbance) was reduced compared to those patients treated with placebo (p<0.01).[3]

INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the improvement of ventricular function and reduction of the incidence of congestive heart failure. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal tract, genitourinary tract, retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention).

The concomitant use of heparin anticoagulation may contribute to the bleeding. Some of the hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial and venous puncture sites, cutdown sites and needle puncture sites).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE®. Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE®, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE®, Alteplase, and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent gastrointestinal or genitourinary bleeding (within 10 days) • Recent trauma (within 10 days) • Hypertension: systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants, e.g., warfarin sodium • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE® are administered.

PRECAUTIONS: General Standard management of myocardial infarction should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided (i.e., internal jugular and subclavian punctures should be avoided to minimize bleeding from noncompressible sites). Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE®. If an anaphylactoid reaction occurs, the infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution. Detectable levels of antibody (a single point measurement) were reported in one patient but subsequent antibody test results were negative.

Laboratory Tests During ACTIVASE® therapy, if coagulation tests and/or measures of fibrinolytic activity are performed, the results may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In

addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole) may increase the risk of bleeding if administered prior to, during or after ACTIVASE®, Alteplase, therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE®. It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding, involving the gastrointestinal tract, genitourinary tract, retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., venous cutdowns, arterial punctures, sites of recent surgical intervention).

The following incidence of significant internal bleeding (estimated as > 250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	< 1%
retroperitoneal	< 1%	< 1%
epistaxis	< 1%	< 1%
gingival	< 1%	< 1%

The incidence of intracranial bleeding (ICB) in patients treated with ACTIVASE® is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Although fatalities due to intracranial bleeding have been observed during and after ACTIVASE® therapy, an analysis of data from three controlled clinical trials in acute myocardial infarction revealed no evidence of increased overall in-hospital mortality. While not statistically significant, in-hospital mortality in patients treated with ACTIVASE®, Alteplase, was lower (4.7%, 11/232) compared to patients not receiving ACTIVASE® (6.8%, 11/162).[3]

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin which is part of the hemostatic plug formed at needle puncture sites will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites, e.g., catheter insertion sites, arterial puncture sites.

Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of myocardial infarction and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: Administer ACTIVASE® as soon as possible after the onset of symptoms.

Lysis of coronary artery thrombi has been documented in 71% of patients treated with ACTIVASE® within 6 hours of onset of symptoms.[1] Improvement of ventricular function and reduction of the incidence of congestive heart failure have been documented in patients treated within 4 hours of the onset of symptoms.[2]

ACTIVASE® is intended for administration by intravenous infusion only.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.[6]

A DOSE OF 150 MG OF ACTIVASE®, ALTEPLASE, SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 48 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Reconstitution should be carried out using a large bore needle (e.g., 18 gauge), directing the stream of Sterile Water for Injection, USP into the lyophilized cake. Slight foaming upon reconstitution is not unusual; standing undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for direct intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE®, Alteplase, may be administered as reconstituted at 1.0 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass bottles are acceptable. ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE®. Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum.

Each 20 mg ACTIVASE® vial (11.6 million IU) is packaged with diluent for reconstitution. (20 mL Sterile Water for Injection, USP): NDC 50242-044-12.

Each 50 mg ACTIVASE® vial (29.0 million IU) is packaged with diluent for reconstitution. (50 mL Sterile Water for Injection, USP): NDC 50242-044-13.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

ACTIVASE®, Alteplase, recombinant
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GENENTECH, INC.
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Comparison of Two Dose Regimens of Intravenous Tissue Plasminogen Activator for Acute Myocardial Infarction

ERIC J. TOPOL, MD, BARRY S. GEORGE, MD, DEAN J. KEREIAKES, MD, RICHARD J. CANDELA, MD, CHARLES W. ABBOTTSMITH, MD, DAVID C. STUMP, MD, JANE M. BOSWICK, MPH, RICHARD S. STACK, MD, ROBERT M. CALIFF, MD, and the TAMI Study Group*

Two dosing schedules of intravenous tissue plasminogen activator (t-PA) for acute myocardial infarction were compared in a multicenter trial. At 2.95 ± 1.1 hours from onset of chest pain, 386 patients received 150 mg of intravenous t-PA. For the first 178 patients (group A), 60 mg were given in the first-hour dose and the remaining 90 mg were infused over 7 hours. In the subsequent 208 patients (group B), the first-hour dose was 1.0 mg/kg and the remaining 150 mg were given over 5 hours. At initial angiography 94 ± 30 minutes into therapy, the infarct vessel patency was 64% in group A versus 75% in group B ($p = 0.02$). By final angiography with up to 4 selective contrast injections, patency was 68% versus 77%, respectively ($p = 0.06$). Repeat angiography at 7 to 10 days demonstrated reocclusion in 17% of group A and 13% of group B patients ($p = 0.35$). There was no difference in fibrinogen nadir or mean hematocrit drop between the 2 groups: 120 mg/dl and 11 points, respectively, in group A compared with 120 mg/dl and 10 points in group B. However, bleeding was reduced in group B patients as evident by a decrease in requirement for ≥2 units of packed red blood cell transfusion (group A 36%, group B 27%, $p = 0.05$) and lower incidence of gastrointestinal bleeding (group A 12%, group B 4%, $p = 0.002$). To further study the importance of weight adjustment, patients were divided into 2 groups according to weight (≤90 kg versus >90 kg). According to the results, lighter weight patients had greater transfusion requirements (35% versus 20%, $p = 0.006$) and more frequent major bleeding episodes (16% versus 7%, $p = 0.025$). Thus, a higher, weight-adjusted first-hour dose of intravenous t-PA, with a shorter duration of maintenance infusion, is associated with: (1) improved infarct vessel patency; (2) more rapid recanalization; and (3) less bleeding complications without more fibrinogenolysis.

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Since the clinical introduction of recombinant tissue-type plasminogen activator (t-PA) for myocardial infarction in 1984, there has been considerable growth in our understanding of its pharmacology and a significant change in production methods. Although very low doses of intravenous t-PA were initially used for a brief duration (1 to 3 hours),[1-4] more recent trials have employed a larger first-hour dose and a prolonged maintenance infusion.[5,6] The initial studies used a predominant 2-chain form of t-PA which was not suitable for large-scale production. The single-chain form of t-PA subsequently introduced has a clearance 40% more rapid than the original preparation and thereby has required a new pharmacologic evaluation for optimal dosing.[5] Although high doses of this form of intravenous t-PA were demonstrated to promote rapid recanalization,[7] they were associated with an increased rate of serious hemorrhagic episodes which led to a recommendation for a decreased dose.[8,9] Thus, controversy exists as to the optimal dosing of this fibrinolytic enzyme for achieving maximal coronary thrombolytic

From the Department of Internal Medicine, Division of Cardiology, University of Michigan, Ann Arbor, Michigan. This study was supported in part by grants HL35058 and HL01489 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland, and a grant from Genentech, Inc., South San Francisco, California. Manuscript received October 23, 1987; revised manuscript received December 24, 1987, and accepted December 26.

Address for reprints: Eric J. Topol, MD, Division of Cardiology, University of Michigan Medical Center, UH B1 F245, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109-0022.

*The collaborating centers and investigators are listed in the Appendix.

TABLE I Comparison of the Two Dose Regimens

	Group A (n = 178)	Group B (n = 208)
Total dose (mg)	150	150
First-hour dose (10% as bolus)	60 mg	1.0 mg/kg
Maintenance infusion		
Amount (mg)	90	150 − first-hour dose
Duration (hr)	7	5

TABLE II Baseline Characteristics*

	Group A (n = 178)	Group B (n = 206)†
Age (yrs)	56 ± 10	56 ± 11
Men (%)	81	76
Weight (kg)	80 ± 16	83 ± 14
Infarct-related artery (%)		
Left main	1	0
LAD	42	39
LC	14	12
Right	43	49
Time CP → t-PA (hrs)	2.9 ± 1.1	3.0 ± 1.1
No. of narrowed coronary arteries (%)‡		
1	54	52
2	28	28
3	17	18
4	1	2
Systolic blood pressure (mm Hg)	134 ± 25	136 ± 26
Heart rate (beats/min)	82 ± 18	79 ± 19

* There were no significant differences ($p < 0.05$) between groups for the variables listed.

† Although 208 patients were treated with this dosing regimen, 2 did not undergo acute catheterization.

‡ Number of major epicardial vessels with ≥50% stenosis.

CP = chest pain; LAD = left anterior descending; LC = left circumflex.

efficacy with the least possible rate of bleeding complications. The present study was undertaken to determine which of 2 t-PA dosing regimens employed in a multicenter trial was superior in terms of frequency and speed of coronary artery recanalization, effects on hemostasis and the coagulation system, and the importance of weight adjustment.

Methods

The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) study design has been previously described in detail.[10] To summarize, selection criteria were: (1) patients with ≤4 hours of chest discomfort or severe symptoms with a duration of 4 to 6 hours, and ongoing pain; and (2) at least 1 mm of electrocardiographic ST-segment elevation in 2 contiguous leads. Patients were excluded for age >75, recent (<6 months) trauma, surgery or stroke, prolonged cardiopulmonary resuscitation, prior coronary artery bypass grafting, cardiogenic shock and previous transmural infarction in the same area. All patients provided informed consent and the protocol was approved by the institutional review board at the respective clinical site.

In the trial, the predominantly single-chain form of t-PA was used.[5] The first 178 patients received an intravenous t-PA dose based on schedule A: 60 mg in the first hour given as a 6-mg bolus and 54-mg drip, and then 20 mg for each of 2 hours, followed by 10 mg/hr for 5 hours with a total dose of 150 mg. In the subsequent 208 patients (schedule B), the same total dose of 150 mg was administered using weight adjustment and a briefer maintenance infusion as follows: 1 mg/kg for the first hour with 10% as a bolus and a maximum dose of 90 mg, and the remainder of 150 mg over the next 5 hours. The patient's report provided the information on body weight required for dosing. The dose regimens are summarized in Table I.

After initiation of t-PA, the patients were transferred to the cardiac catheterization laboratory of the respective clinical site for acute angiography. Nonionic contrast dye was used. The first contrast injection of the infarct vessel was performed after 60 minutes of therapy and images obtained no later than 90 minutes. An exception to the latter occurred when difficulties arose in obtaining arterial access or interhospital transport was delayed. The final determination of infarct vessel patency was made at 90 minutes, after up to 4 injections of the infarct-related artery.

The perfusion status was classified according to the TIMI (Thrombolysis in Myocardial Infarction Study Group) grading system.[2] For the purpose of this study, TIMI 0 and 1 were considered occluded and TIMI 2 or 3 patent. The angiograms were subsequently reviewed at the core angiographic laboratory for verification of the final TIMI grade determination.

On the basis of the 90-minute infarct vessel angiogram, patients were triaged to 3 different groups as follows: (1) persistent occlusion—coronary angioplasty was considered at the discretion of the investigator; (2) patent, ≥50% residual stenosis, suitable for angioplasty—patients were randomized to undergo the procedure immediately or at 7 days; (3) patent, with coronary anatomy unsuitable for angioplasty. Emergency coronary artery bypass surgery was defined as a direct transfer from the cardiac catheterization laboratory during the acute study to the operating room. The procedure was performed for failed percutaneous transluminal coronary angioplasty or high-risk coronary anatomy. In the first 50 patients from the aforementioned groups 1 and 3, only the first 3 hours of t-PA (100 mg) were infused (all in group A patients). Angioplasty's complete success was defined as <50% residual stenosis and partial success as ≥50% residual stenosis after balloon dilatation.

Concomitant medical therapy consisted of heparin (5,000 U at access, 5,000 U at the time of angioplasty if performed acutely, and 500 to 1,000 U/hr for ≥3 days by continuous infusion adjusted to 2.5 to 3 times the partial thromboplastin time), aspirin (325 mg/day), dipyridamole (75 mg, 3 times daily) and diltiazem (30 to 60 mg, 4 times daily).

At 7 to 10 days, patients underwent repeat cardiac catheterization to determine infarct vessel patency and left ventriculography. Besides the paired studies, patients returned to the catheterization laboratory be-

fore 7 days had elapsed if recurrent ischemia occurred, as defined by ≥20 minutes of chest discomfort associated with electrocardiographic changes. After urgent angiography in these patients, who by now had reached a clinical endpoint, either coronary angioplasty or bypass surgery was performed and followed by a repeat (third) cardiac catheterization, whenever possible, before hospital discharge. Reocclusion was defined by angiographic documentation of flow pattern as TIMI grade 0 or 1 and flow pattern diagnosed subsequent to established perfusion as TIMI 2 or 3.[2]

Bleeding complications were characterized according to: (1) site; (2) need for transfusion of ≥2 units of packed red blood cells for augmentation of hematocrit >30; and (3) baseline and nadir hematocrit values. Gastrointestinal bleeding referred to either guaiac-positive results or frank blood in emesis or stool. Intracranial and retroperitoneal hemorrhage was diagnosed using computed axial tomographic scanning. Assessment of coagulation proteins included assay of the serum fibrinogen by the Clauss and sodium sulfite precipitation methods[11,12] and the fibrinogen degradation product titer[13] by tanned red cell agglutination method at baseline, 3, 8 and 12 hours after t-PA.

Statistical analysis: Values are expressed as mean ± 1 standard deviation unless otherwise specified. Comparison of group A versus group B patients was made using chi-square analysis for dichotomous variables and an unpaired *t* test or Wilcoxon log-rank test, as specified, for continuous variables. The comparison between the 2 dose regimens was performed with and without those 50 patients in group A who received 100 mg instead of 150 mg of t-PA. For analysis of the importance of weight (≤90 or >90 kg), chi-square analysis was used for dichotomous variables, a Wilcoxon rank-sum test for continuous variables and a logistic regression model for testing the relation between the 2 weight groups for multiple variables.

Results

Study population: The relevant demographic characteristics for the 2 patient groups are summarized in Table II. Patients receiving the 2 different dose regimens were similar with regard to the baseline hemodynamic, angiographic and demographic features.

Patency of the infarct vessel: Table III lists the results for acute and follow-up (before discharge) infarct vessel perfusion status. A significantly higher patency was demonstrated for group B patients at the initial angiogram. As demonstrated in Figure 1, nearly all patients in group B who demonstrated infarct vessel recanalization were already patent at the initial angiogram. The residual stenosis of the infarct vessel was significantly decreased in group B patients compared with group A (Figure 2). The results for initial angiographic patency excluding the 50 patients in group A who did not receive the full 150 mg t-PA dose were: group A, 68% patent; group B, 75% patent; p = 0.16.

Acute coronary angioplasty was performed in 89 patients in group A and 93 patients in group B with complete or partial success in 73% versus 83%, respectively (p = 0.09). Emergency bypass surgery was necessary in 8% of group A patients compared to 4% in group B (p = 0.09). During hospitalization, a total of 39 (22%) bypass surgery procedures were performed in group A compared with 44 (21%) in group B (p = 0.19). Intraaortic balloon counterpulsation was used in 11% of group A versus 6% of group B patients (p = 0.09).

Bleeding complications and coagulation system effects: The transfusion requirement, admission and nadir hematocrits, and incidence of bleeding by site appear in Table IV. As shown, the frequency of gastrointestinal bleeding was significantly higher in group A patients. Only 2 patients (both in group B) developed intracranial hemorrhage. Both patients were female with a history of longstanding hypertension, age 68 and 73, respectively.

In Figure 3, the serum fibrinogen values are plotted for the 2 dosage regimens. There was no difference in the nadir fibrinogen level (120 mg/dl for both groups). The median peak FDP titer was 1:16 in group A versus 1:32 for group B.

Influence of body weight: Patients were divided into 2 groups as shown in Table V. The baseline weight was not recorded in 5 patients enrolled in the trial. As expected, there was a significantly lower proportion of males in the ≤90-kg weight column. There were no differences (p <0.05) in patency of the infarct vessel, infarct location, presence of multivessel disease, group A or B dosing or bypass surgery. Lighter weight patients underwent acute coronary angioplasty less fre-

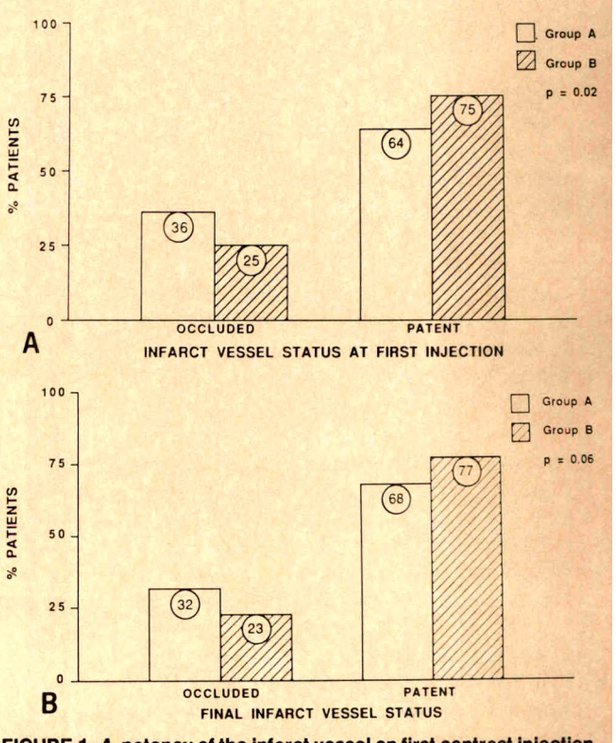

FIGURE 1. *A*, patency of the infarct vessel on first contrast injection. Group B patients demonstrated a significantly higher patency rate. *B*, patency of the infarct vessel after up to 4 injections at 90 minutes of tissue plasminogen activator (t-PA) therapy. A trend of higher patency was observed for group B patients.

TABLE III Patency of the Infarct Vessel

	Group A (n = 178)	Group B (n = 206)	p Value
Initial angiogram			
Time (min)	94 ± 31	95 ± 31	0.61
TIMI 2 or 3	110/173 (64%)	153/205 (75%)	0.02
Final angiogram*			
TIMI 2 or 3	119/167 (68%)	157/205 (77%)	0.06
Recurrent ischemic events	50 (28%)	56 (27%)	0.76
Reocclusion on follow-up angiogram (1 week)	30 (17%)	28 (13%)	0.24

* Final angiogram after up to 4 injections of the infarct vessel at the 90-minute point of t-PA therapy.

TIMI 2 or 3 = Thrombolysis in Myocardial Infarction Study Group's grade 2 or 3 (perfusion status patent).

quently (45 versus 58%, respectively, p = 0.023) and had a higher success rate for angioplasty (84 versus 68%, p = 0.06).

Despite less invasive procedures performed in the lighter weight patient group (equivalent to a 21% bypass surgery rate during hospitalization, less acute angioplasty), their transfusion requirement was higher, with major bleeding episodes more frequent as confirmed by a significantly lower nadir hematocrit (Table V). In addition, these patients had a lower nadir plasma fibrinogen and a decreased likelihood of reocclusion.

Discussion

In the current study, 2 different t-PA dose regimens with the same 150 mg cumulative dose were compared. The second regimen, which provided for a weight-adjusted first-hour dose and a lesser duration of maintenance infusion, was found to be superior with respect to frequency and rapidity of infarct vessel patency, decreased transfusion requirement and overall bleeding complications, without more extensive fibrinogenopenia.

Comparison with previous studies: There have been 3 previous trials using the single-chain preparation of t-PA. In the randomized trial of Topol et al,[5] 0.75 mg/kg of t-PA was given over the first hour and 0.25 mg/kg per hour over the subsequent 2 hours. Infarct vessel patency at 90 minutes was 69% and increased to 79% at 120 minutes. Using criteria for bleeding complications similar to those adopted in the current study, 29% received transfusion, gastrointestinal bleeding occurred in 1.1%, genitourinary bleeding in 5% and the fibrinogen nadir was 62% of baseline. Reocclusion was not systematically determined but the angiographically confirmed incidence was 20%. As recently reported by Mueller et al,[7] the open-label Thrombolysis in Myocardial Infarction (TIMI) multicenter trial was divided into 5 separate groups (A through E). In the E phase, 167 patients received a dose of 90 mg over the first hour and 60 mg over the subsequent 4 hours. A high rate of infarct vessel patency resulted (85% at 120 min), albeit accompanied by a 1.6% incidence of intracranial hemorrhage. This resulted in a recommendation for a lower dose: 60 mg in the first hour and a cumulative dose of 100 mg.[8]

The dose of 150 mg used in the TAMI trial achieved a high proportion of infarct vessel patency without inducing an unacceptable rate of serious bleeding episodes. Although the overall transfusion rate and periaccess bleeding incidence was somewhat higher compared to other trials, all TAMI patients underwent emergent angiography per protocol, with a significant proportion (21%) undergoing coronary artery bypass surgery. Nearly all of these patients received transfusion.

First-hour dose: The dose of t-PA in the first hour appears to be a critical determinant of the time of recanalization. As previously demonstrated by TIMI with baseline angiography, increasing the dose from 50 to 90 mg did not yield significantly higher patency at 90 minutes of therapy, but the speed of achieving reperfusion was markedly enhanced.[7] In the current trial, the higher first-hour dose used in group B was associated with more rapid recanalization and a trend

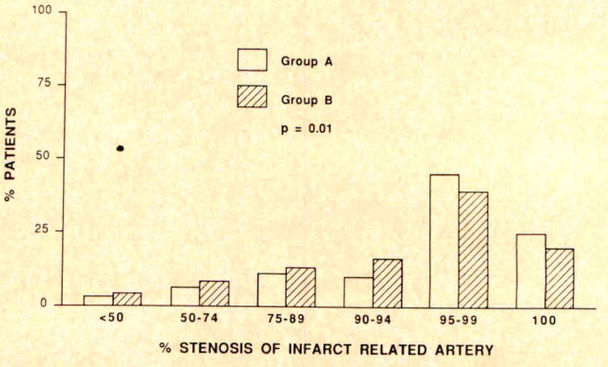

FIGURE 2. Infarct-related artery percent diameter stenosis for group A versus group B patients at the final angiogram obtained during the acute study. A comparison of group A with group B patients shows an overall higher grade residual stenosis for group A.

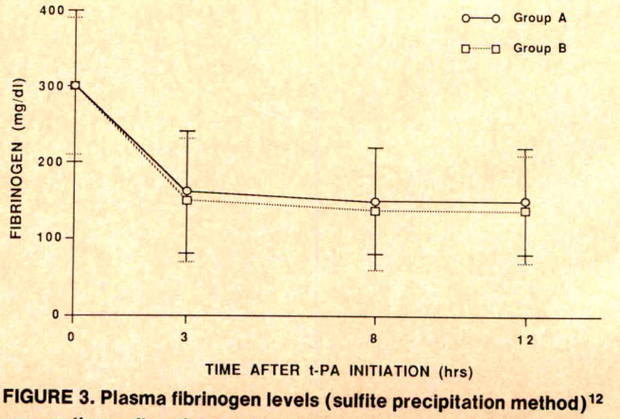

FIGURE 3. Plasma fibrinogen levels (sulfite precipitation method)[12] versus time after tissue plasminogen activator (t-PA) therapy. There were no significant differences between the 2 dose groups for nadir fibrinogen values.

toward a higher proportion of infarct vessel patency at the final angiogram.

Weight adjustment: The results of this study further confirm the importance of a weight-adjusted dose of t-PA. In previous studies by Topol et al[14] and Gold and co-workers,[6,15] the utility of a weight-adjusted dose and its increased safety have been demonstrated. Even though a higher dose was employed in TAMI's group B patients, an overall decreased bleeding complication rate resulted which likely reflects weight adjustment. Patients weighing <90 kg had a definite increased risk of bleeding complications compared with heavier patients. In contrast, with a higher weight-adjusted first-hour dose of t-PA, there was an increase in rate and proportion of infarct vessel patency. Thus, in order to avoid bleeding episodes and a high transfusion requirement, patients weighing <60 kg should probably receive a lower than 60 mg first-hour dose of t-PA. Group B data suggest that patients weighing up to 90 kg derive benefit from the higher dose in terms of coronary recanalization. Because doses >90 mg were not given in the first hour, the relative effects of thrombolysis versus hemorrhage remain speculative in patients >90 kg.

Maintenance infusion: As demonstrated by Gold et al,[6] the purpose of the maintenance infusion is to increase the extent of coronary thrombolysis and limit rethrombosis. The ideal length and dose requirement of such a prolonged infusion have not yet been determined. In 1 recent study, too long an infusion has been reported to yield a high rate of periaccess bleeding that may be unacceptable,[16] whereas in a recent multicenter trial with a predominant 2-chain form of t-PA, up to a 24-hr low-dose infusion has been tested with apparent low reocclusion and bleeding rate complication.[17]

In the current trial, a possible explanation for the increased bleeding observed in patients from group A is the lack of weight adjustment and the duration of maintenance infusion for 7 rather than 5 hours (group B). The additional 2 hours of maintenance infusion may be significant, as reflected by the 3-fold increase in gastrointestinal bleeding in group A, most of which was initially manifest during the infusion. The increased bleeding with longer maintenance infusions may reflect sustained fibrinolytic action of t-PA. Although the half-life of this t-PA preparation is <3 minutes,[5] the beta phase half-life is more than 20 minutes[18] and this ongoing fibrinolysis proceeds despite physiologic plasma levels of t-PA.[19] It would therefore be anticipated that in group A patients there was a considerably longer pharmacologic fibrinolytic effect. Because reocclusion was actually not increased in group B patients, our data suggest that a shorter maintenance infusion of 5 hours may be preferable to 7 hours in achieving the purpose of limiting rethrombosis without promoting bleeding.

Effects of dose on angioplasty success rate: A trend toward a higher success rate in acute coronary angioplasty was observed among group B patients, along with a decrease in the need for emergency bypass surgery. Although this observation may theoretically be attributed to enhanced coronary thrombolysis (with facilitation of the dilatation procedure), it also may be related to a learning curve phenomenon during the TAMI trial. This point brings up the chief limitation of the current study: although a relatively large sample size at each of the 2 dose schedules was studied, this was a consecutive series and not a randomized comparison. Selection of patients for randomization to angioplasty was determined by the investigators. During the course of the trial, a trend toward decreased randomization to angioplasty and less need for emergency bypass surgery was noted, so that it remains unclear whether the dose change actually served as a pivotal factor for angioplasty success.[20]

TABLE IV Bleeding Complications

	Group A (n = 178)	Group B (n = 206)
Transfusion >2 U PRBC	64 (36%)	56 (27%)*
Admission hematocrit (%)	43 ± 6	44 ± 4
Nadir hematocrit (%)	31 ± 6	32 ± 5
Gastrointestinal bleeding	21 (12%)	8 (4%)†
Intracranial bleeding	0 (0%)	2 (0.9%)
Retroperitoneal bleeding	1 (0.6%)	1 (0.5%)

* p = 0.05.
† p = 0.002.
U PRBC = units of packed red blood cells.

TABLE V Effect of Body Weight on Bleeding, Coagulation Factors and Rethrombosis

	≤90 kg	>90 kg	p Value
No.	285	96	—
Men*	210 (74%)	90 (94%)	<0.001
Transfused ≥2 U PRBC	99 (35%)	19 (20%)	0.006
Major bleeding†	47 (16%)	7 (7%)	0.025
Reocclusion	37 (13%)	21 (22%)	0.036
Nadir Hct (median)	31	33	0.0005‡
Nadir fibrinogen (mg/dl) (median sulfite)	150	179	0.0007‡

* Regression analysis has shown that lighter weight, independent of female sex, was associated with increased bleeding risk.[21]
† Major bleeding refers to observed blood loss >150 ml.
‡ Continuous variables were analyzed using the Wilcoxon rank-sum test.
Hct = hematocrit; U PRBC = units of packed red blood cells.

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Appendix
Participating Institutions/Investigators

University of Michigan: Eric J. Topol, MD (principal investigator), William W. O'Neill, MD, Joseph A. Walton, MD, Eric R. Bates, MD, Stephen G. Ellis, MD, M. Anthony Schork, PhD, Eva Kline, RN, BSN, Laura Gorman, RN, BSN, Raymond Worden, BS, Bertram Pitt, MD, and satellite centers in Foote Hospital, Jackson, Michigan: Gregory Baumann, MD, John Maino, MD, Mary Ann Mengleson, MD, Constance Doyle, MD, Patricia Lamb, MD, and South Macomb Hospital, Warren, Michigan: Stanley Wolfe, MD, Leonard Bayer, DO, Armando Madrazo, MD, Robert Moore, MD; Duke University: Robert M. Califf, MD (co-principal investigator), Richard S. Stack, MD, Harry R. Phillips III, MD, Tomoaki Hinohara, MD, Robert H. Peter, MD, Ken Morris, MD, Victor Behar, MD, Y. Kong, MD, Charles Simonton, MD, Thomas Bashore, MD, Eric Carlson, MD, Susan Mantell, RN, BS, Jane M. Boswick, MPH; Riverside Methodist Hospital: Barry S. George, MD, Richard J. Candela, MD, Joanne Dillon, RN, BS, Ramona Masek, RN, BS; Christ Hospital: Dean J. Kereiakes, MD, Charles W. Abbottsmith, MD, Linda Anderson, RN, BSN, Linda Martin, RN, BSN; William Beaumont Hospital: Gerald C. Timmis, MD, Renato Ramos, MD, V. Gangadharan, MD, Cindy Tollis, RN, BSN; Duke University, Biostatistical Core Laboratory: Jane M. Boswick, MPH, Lynne Aronson, BS, Kerry L. Lee, PhD, Robert M. Califf, MD; University of Michigan, Core Angiographic Laboratory: Raymond Worden, BS, Cindy L. Grines, MD, Mark Sanz, MD, Eric J. Topol, MD; Data Monitoring Committee: Mark Hlatky, MD, Daniel B. Mark, MD, MPH, Kerry L. Lee, PhD; University of Vermont, Core Hematology Laboratory: David Stump, MD, Desire Collen, MD, PhD, Dajnija Thornton, BS.

Evaluation of a QRS Scoring System for Estimating Myocardial Infarct Size. VI: Identification of Screening Criteria For Non-Acute Myocardial Infarcts

WILLIAM D. ANDERSON, BA, NANCY B. WAGNER, BA, KERRY L. LEE, PhD, RICHARD D. WHITE, MD, JAMES YUSCHAK, MD, VICTOR S. BEHAR, MD, RONALD H. SELVESTER, MD, RAYMOND E. IDEKER, MD, PhD, and GALEN S. WAGNER, MD

Each of the 54 criteria in the Selvester 32-point QRS scoring system for estimation of myocardial infarct (MI) size has attained ≥95% specificity in normal subjects. This study was performed to identify a subset of those criteria with cumulative specificity ≥95% and maximal sensitivity for use in screening for the presence of non-acute MI. Coronary angiography and left ventriculography were used to identify 500 normal subjects, 60 patients with isolated anterior MI and 62 patients with isolated inferior MI. Patients with the QRS confounding factors of ventricular hypertrophy, fascicular block or bundle branch block on their electrocardiogram were not included. Using stepwise logistic regression analysis, the screening criteria identified were: (1) Q ≥30 ms in aVF, (2) R ≤10 ms and ≤0.1 mV in V_2 and (3) R ≥40 ms in V_1. Cumulatively, these 3 screening criteria achieved 84% and 77% sensitivities for inferior and anterior MI groups, respectively. Thus, a set of 3 criteria from the Selvester QRS scoring system is capable of identifying single non-acute anterior or inferior MI in 80% of patients, and falsely indicating presence of MI in only 5% of normal subjects.

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For more than half a century, the 12-lead electrocardiogram has been the standard for determining both the presence and location of a myocardial infarct (MI). However, the commonly used electrocardiographic criteria for MI diagnosis have proven to be relatively insensitive. Previous studies from this institution have compared the sensitivities of standard electrocardiographic and vectorcardiographic criteria.[1,2] From the electrocardiogram, sensitivities ranging from 28% to 44% for inferior MI criteria and from 43% to 60% for anterior MI criteria were identified. In contrast, vectorcardiographic criteria attained sensitivities of 82% and 95% for inferior and anterior MI locations respectively, suggesting there is additional MI diagnostic capability in the QRS complex beyond that attained by established electrocardiographic criteria.

Selvester et al[3–5] designed computer simulations of the human heart activation sequence to identify the changes in the QRS complex occurring with various sized infarcts in the distributions of the 3 primary coronary arteries. This information was used to develop a 54 criteria/32 point QRS scoring system based on the electrocardiogram for estimating MI size, with each point representing approximately 3% of the left ventricle.[6] The present study utilizes the Selvester scoring system to: (1) identify a subset of criteria that retain high cumulative specificity in normal subjects and achieve maximal sensitivity in patients with single non-acute anterior or inferior MI, and (2) compare the

From the Department of Medicine, Division of Cardiology, Duke University Medical Center, Durham, North Carolina. This work was supported in part by research grant HL-17670 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received September 8, 1987; revised manuscript received and accepted December 23, 1987.

Address for reprints: Galen S. Wagner, MD, Box 31211, Duke University Medical Center, Durham, North Carolina 27710.

performance of the resultant "screening" criteria to established vectorcardiographic criteria.

Methods

Patient selection: *Normal population:* The previously reported normal population consists of 500 subjects with 50 men and 50 women in each of the 5 decades between ages 20 and 69.[6] These subjects were either healthy volunteers younger than 40 years of age or patients with chest pain who underwent cardiac catheterization and were shown to have neither significant coronary arterial stenosis nor left ventricular wall motion abnormalities. Patients were also required to have either left ventricular ejection fraction >50% or left ventricular end-diastolic pressure ≤12 mm Hg. Patients whose electrocardiograms showed evidence of left or right bundle branch block, left or right ventricular hypertrophy or left anterior or posterior fascicular block were excluded.

Myocardial infarction populations: The Duke University Medical Center computerized data bank[7] was searched to identify patients with a single non-acute anterior or inferior MI, and available vectorcardiograms and electrocardiograms. There were 60 patients with an "anterior MI"[2] defined by the simultaneous presence of a ≥75% diameter stenosis of the left anterior descending coronary artery and akinesia or dyskinesia of the anterior wall on the right anterior oblique ventriculogram. There were 62 patients with an "inferior MI"[1] defined by the presence of ≥75% diameter stenosis of the right coronary artery in conjunction with akinesia or dyskinesia of the inferior wall. The validity of these criteria for identifying MI has been previously established by comparison with postmortem hearts.[8] Patients were excluded if catheterization showed evidence of valvular or congenital heart disease or the pulmonary artery mean pressure was ≥25 mm Hg.

Both the Frank lead vectorcardiograms and the standard electrocardiogram of all MI patients had been obtained within 3 days of catheterization. Patients were excluded for electrocardiographic evidence of right ventricular hypertrophy, left anterior or posterior fascicular block or left or right bundle branch block. They were also excluded for either electrocardiographic or vectorcardiographic evidence of left ventricular hypertrophy.[1,2]

Electrocardiographic and vectorcardiographic evaluations: All electrocardiograms were evaluated using the complete Selvester QRS scoring system. This system and its method of application have been described in detail elsewhere.[6] Measurements of amplitude are reported in mV (1 mm = 0.1 mV) and duration is reported in ms (1 mm = 40 ms). The vectorcardiograms were evaluated using the criteria previously described by Starr et al.[1,2] Each set of vectorcardiographic criteria has been reported to achieve ≥95% specificity in a group of normal subjects with characteristics similar to the normal population described in the present study.

Data analysis: A stepwise logistic regression analysis was used to identify a subset from the 54 criteria that would have maximal ability to discriminate between the patients with either anterior or inferior MI and the normal subjects. The first step selected the single criterion that attained the highest sensitivity. Further steps identified additional criteria that added the greatest increments of sensitivity while retaining the cumulative specificity of the screening group at a level of ≥95%. If 2 or more criteria indicative of MI in the same location were equally sensitive, both their individual and combined effects on the performance of the screening group were considered.

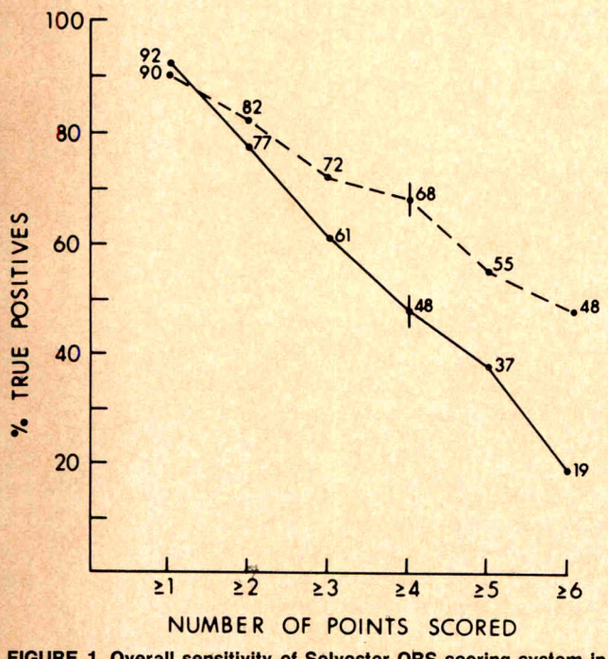

FIGURE 1. Overall sensitivity of Selvester QRS scoring system in inferior (n = 62) and anterior (n = 60) myocardial infarct (MI) populations. Specificity level ≥95% was maintained by requiring ≥4 points. At this level, 68% of anterior MI group (*dashed line*) and 48% of inferior MI group (*continuous line*) were identified.

Results

When ≥1 point was required for MI detection using the complete scoring system, sensitivities of 92% and 90% were achieved in the inferior and anterior MI populations, respectively (Figure 1). However, this system has been previously reported to require ≥4 points to achieve ≥95% specificity.[6] This ≥4 point level attained sensitivities of only 48% in the inferior MI population and 68% in the anterior MI population.

Table I lists the performances of the most sensitive individual criteria. A Q wave ≥30 ms in lead aVF was the single most sensitive criterion, identifying 45% of the combined MI populations. Nine other criteria identified between 25% and 33% of the combined populations.

Table II lists the results of the stepwise logistic regression analysis. When the R-wave duration or amplitude criteria in lead V_2 were added to the Q-wave criterion in lead aVF, sensitivities of 75% were

achieved for each. The cumulative specificities decreased to 96% with each criterion individually but only to 97% when both the R-wave duration and amplitude criteria were considered together. In step III, the criterion of R wave ≥40 ms in lead V_1 added the greatest further increase in sensitivity. The specificity decreased to <95% when the 2 R-wave criteria in lead V_2 were considered separately. Only when these were combined (R wave in V_2 ≤10 ms and ≤0.1 mV) was the cumulative specificity of the screening set maintained at the required specificity standard.

The performances of each of the screening criteria considered independently for the 2 MI locations are listed in Table III. In 49 of the 55 times the Q wave ≥30 ms in lead aVF was satisfied (89%), the MI was inferior. This criterion was 79% sensitive in screening for inferior MI, identifying 49 of the 62 patients. In 41 of these 49 patients (84%), the Q wave ≥30 ms in aVF was the only screening criterion satisfied.

The combined R-wave duration and amplitude criteria in lead V_2 were associated only with the anterior MI location. These criteria achieved individual sensitivities of 67% and 65% in the anterior MI population, respectively, and when combined attained a cumulative sensitivity of 65%.

The R wave ≥40 ms criterion in lead V_1, which is usually associated with posterolateral MI location,[10] was met by both patients with inferior (n = 11) and anterior (n = 5) MI locations.

In Figure 2, the sensitivity of the screening criteria group (≥1 point) is compared to the sensitivities of the entire Selvester scoring system (≥4 points) and the vectorcardiographic criteria. In the inferior MI population, the sensitivity of the screening criteria equals that of the vectorcardiographic criteria (84%) and is superior to that of the complete scoring system. For the anterior MI group the screening criteria achieve a sensitivity superior to the sensitivities of both the vectorcardiographic criteria (77% vs 72%) and the complete scoring system (77% vs 68%).

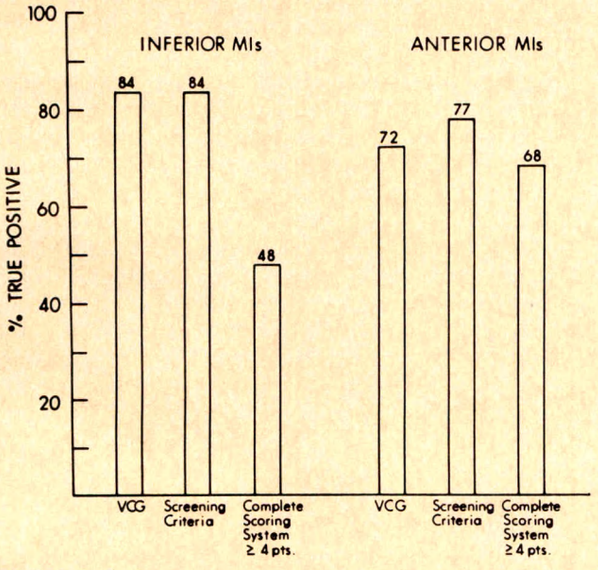

FIGURE 2. Performance of screening criteria versus established vectorcardiographic (VCG) criteria and entire Selvester QRS scoring system (≥4 points). VCG and screening criteria identified 84% of inferior MI group compared to 48% detected by the complete scoring system. In the anterior myocardial infarction (MI) population, the screening criteria (77%) were superior to both the VCG criteria (72%) and the entire Selvester QRS scoring system (68%).

TABLE I Sensitivities of Individual Criteria

Lead	Criterion	Sensitivity (%)
aVF	Q ≥30 ms	45
V_2	R ≤10 ms	33
V_2	R ≤0.1 mV	32
aVF	R/Q ≤2	31
V_3	R ≤20 ms	30
V_4	R ≤0.7 mV	30
V_1 and V_2	RV_2 ≤ RV, (mV)	30
II	Q ≥30 ms	28
V_4	R/S ≤1	26
V_1	any Q	25
aVF	Q ≥40 ms	22
V_2	any Q	22
V_3	any Q	21
V_5	R ≤0.7 mV	21
V_6	R ≤0.6 mV	20
aVF	R/Q ≤1	19
V_4	R/S ≤0.5	19
V_5	R/S ≤2	19
V_4	Q ≥20 ms	18
aVL	Q ≥30 ms	16
V_1	R ≥40 ms	13
V_6	Q ≥30 ms	12
V_6	R/S ≤3	12

TABLE II Logistic Regression Analysis: Identification of Screening Criteria

Step	Screening Criteria	Cumulative Sensitivity (%)	Cumulative Specificity (%)
I	aVF Q≥30 ms	45	98
II	aVF Q ≥30 ms V_2 R ≤10 ms	75	96
	aVF Q ≥30 ms V_2 R ≤0.1 mV	75	96
	aVF Q ≥30 ms V_2 R ≤10 ms* V_2 R ≤0.1 mV*	75	97
III	aVF Q ≥30 ms V_2 R ≤10 ms* V_2 R ≤0.1 mV* V_1 R ≥40 ms	80	95

* Both criteria must be satisfied.

Discussion

Effective electrocardiographic criteria for the identification of non-acute MI should be easy to apply and should achieve both high specificity and sensitivity. The need for improved electrocardiographic criteria clearly exists, as traditional criteria have been shown to be insensitive. Hurd et al[10] demonstrated sensitiv-

TABLE III Performance of Screening Criteria

Lead	Criterion	Inferior MI (n = 62) Criterion Met No. (%)	Inferior MI (n = 62) Only Criterion Met (n)	Anterior MI (n = 60) Criterion Met No. (%)	Anterior MI (n = 60) Only Criterion Met (n)
aVF	Q ≥30 ms	49 (79)	41	6 (10)	2
V_2	R ≤10 ms	0	0	40 (67)	1
V_2	R ≤0.1 mV	0	0	39 (65)	0
V_2	R ≤10 ms* R ≤0.1 mV*	0	0	39 (65)	37
V_1	R ≥40 ms	11 (18)	3	5 (8)	4

* Both criteria must be satisfied.
MI = myocardial infarct; ( ) = % of either inferior or anterior MI population.

ities from 4% to 34% for 3 different sets of criteria for the identification of inferior MI, a marked contrast with the 82% sensitivity achieved by the vectorcardiographic criteria of Starr et al.[1] A similar disparity has been reported between traditional electrocardiographic criteria and the vectorcardiographic criteria of Starr et al[2] for anterior MI. Warner et al[11,12] have reported high sensitivities using new electrocardiographic criteria in both inferior and anterior MI populations. However, the Warner criteria for inferior MI diagnosis require an electrocardiogram of exceptional quality and may, therefore, be difficult to apply routinely. The Warner criterion for anterior MI detection is similar (R duration <20 ms in lead V_2) to the R duration criterion identified in the present study. The quality of the electrocardiograms and the limitations of manual measurement techniques preclude comparison with the Warner anterior MI criteria.

The need for improved diagnostic criteria from the electrocardiogram is not met by use of the complete Selvester QRS scoring system. The high point score (≥4 points) required to meet specificity standards renders the system too insensitive for the identification of MI. The 3 proposed screening criteria achieve both a specificity of 95% and high sensitivity. Their application effectively distinguishes between patients with or without MI, indicating the group for whom all of the criteria of the complete Selvester QRS scoring system can be appropriately applied for estimating MI size.

The selection of MI populations defined by clinical parameters from cardiac catheterization rather than from direct anatomic observations may have diminished the sensitivities of both the electrocardiographic and vectorcardiographic criteria in this study. A ventriculographic/anatomic correlation study by Ideker et al[8] showed that while hypokinesia was frequently not associated with any fibrosis, there was always some fibrosis in those ventricular walls that had demonstrated either akinesia or dyskinesia. However, it is still possible that some of the patients in the MI groups had no infarcted myocardium. When the Selvester scoring system is used to identify MI with the minimal point requirement ≥1, sensitivities of 92% and 90% are obtained in the inferior and anterior MI populations, respectively. Thus approximately 10% of both MI populations fail to satisfy any QRS scoring criterion, suggesting the absence of any infarction. Postmortem anatomic studies will be required to determine the true sensitivity of the screening criteria identified in the present study.

Because patients with confounding electrocardiographic abnormalities were excluded, the screening criteria can be applied with confidence only to electrocardiograms without evidence of ventricular hypertrophy, fascicular block or bundle branch block. Further studies are necessary to evaluate the performance of the screening criteria in patients with such abnormalities. However, diminished R waves in lead V_2 are common in left ventricular hypertrophy and left bundle branch block, and increased R waves in lead V_1 are common in right ventricular hypertrophy and right bundle branch block. New sets of screening criteria will therefore be necessary in the presence of these factors.[13]

Only anterior and inferior MI locations were included in this study because they occur most commonly and can be reliably detected on the right anterior oblique view of the left ventriculogram. Future studies will be required to develop screening criteria for MI in the posterolateral myocardium, commonly in the distribution of the left circumflex coronary artery. However, the criterion of R ≥40 ms in V_1 identified in this study may be quite useful.

The screening criteria proposed in this study compare favorably with the previously developed vectorcardiographic criteria of Starr et al.[1,2] In the inferior MI population the screening criteria equalled the sensitivity of the vectorcardiogram (84%), and in the anterior MI population it was exceeded (77% vs 72%). These results are particularly significant when the clinical prevalence of the standard 12-lead electrocardiogram is considered.

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Development and Validation of an Automated Method of the Selvester QRS Scoring System for Myocardial Infarct Size

JAMES E. POPE, MD, NANCY B. WAGNER, BA, DAVID DUBOW, BS,
JOHN H. EDMONDS, MD, GALEN S. WAGNER, MD,
and W. KENNETH HAISTY, Jr., MD

The Selvester QRS score for estimation of myocardial infarct (MI) size from the standard 12-lead electrocardiogram (ECG) has not yet achieved wide recognition as a valuable tool in the routine assessment of the MI patient, primarily because of the practical limitations inherent to manual application. This study examined the ECGs of 438 patients (105 normal subjects, 161 with "possible" MI and 172 with "definite" MI based on data from cardiac catheterization) to develop software for an automated method of the Selvester system in attempts to overcome the manual constraints. After a comprehensive validation process involving extensive interactions between the manual scorer and the software developer, an automated method of the Selvester system was generated that had a high correlation with manual application (r = 0.94) and was superior regarding time, training, reader bias, reproducibility and precision of measurement. These results indicate that an automated version of the Selvester QRS scoring system would resolve many of the limitations of manual application and would provide a reliable, technically accurate estimate of MI size that could be incorporated into ECG diagnostic programs and used in standard digital ECG machines.
(Am J Cardiol 1988;61:734–738)

The Selvester QRS scoring system[1] is an established method for estimating the size of a single myocardial infarction (MI) in the distribution of the 3 major coronary arteries based on quantitative QRS changes from the standard 12-lead electrocardiogram (ECG). This system has been tested for intra- and interobserver variability,[2] validated through comprehensive anatomic correlations[3–5] and refined to yield a complete 54-criteria/32-point QRS scoring system[6] with 98% specificity at a threshold of ≥4 points in an extensive normal population equally distributed by age and sex (Figure 1).

From the Departments of Medicine, Wake Forest University Medical Center, Winston-Salem, and Duke University Medical Center, Durham, North Carolina. This work was supported in part by research grant HL-17670 from the National Heart, Lung, and Blood Institute, the National Institutes of Health, Bethesda, Maryland. Manuscript received October 5, 1987; revised manuscript received and accepted December 23, 1987.

Address for reprints: Galen S. Wagner, MD, Box 31211, Duke University Medical Center, Durham, North Carolina 27710.

Although the Selvester system has been evaluated in a variety of studies,[7–14] and the method for its manual application described in detail,[15] it has not yet experienced general clinical acceptance. The system is limited by the tediousness of performing precise manual measurements, the training necessary to perform these measurements correctly, the reproducibility of results, the time necessary to score individual ECGs and the bias of the reader. A digital computer for ECG analysis programmed to apply the Selvester criteria would likely resolve these limitatioins. Once validated, and the strengths and weaknesses understood, an automated scoring method could be incorporated into ECG diagnostic programs and used in standard digital ECG machines. This study was performed to develop and validate software for an automated method of Selvester QRS scoring.

Methods

Patient population: Consecutive patients who had elective cardiac catheterization for the evaluation of chest pain at North Carolina Baptist Hospital of the

Wake Forest University Medical Center between November 1981 and June 1983 were considered for this study. Patients were excluded for prior cardiac surgery, evidence of valvular heart disease and historical or wall motion study evidence of prior MI. Patients were also excluded for ECG evidence of right or left bundle branch block, left anterior or posterior fascicular block, left or right ventricular hypertrophy, paced rhythm or ventricular preexcitation. Ninety-eight percent of the ECGs were recorded within 2 days before cardiac catheterization.

Of the 438 patients who formed the final study group, the mean age was 53 years, and 71% were men. Data from cardiac catheterization revealed 105 patients with no obstructive coronary artery disease or left ventricular wall motion abnormalities. There were 161 patients with "possible" evidence of a single MI suggested by a localized area of hypokinesis, and 172 with "definite" evidence of a single MI as supported by localized akinesis or dyskinesis. Patients classified as a "possible MI" or "definite MI" were also required to have an obstructive coronary lesion in the vessel supplying the region of the wall motion abnormality.

Every alternating fourth or fifth ECG (n = 93) was duplicated from the study group and randomly distributed among the population. These were subsequently matched to their originals, thus forming a set of 186 ECGs, and used for determination of blinded intraobserver agreement in the manual scoring method.

Study design: *Manual application:* Manual QRS scoring was performed on 3-channel ECGs (at a paper speed of 25 mm/s and standard gain) obtained by a Marquette recorder by an investigator at Duke University Medical Center experienced in the application of the system. The method for manual application has been described previously in detail.[6,15] All criteria satisfied and a final score for each ECG were entered into a microcomputer for subsequent comparison with automated scoring.

The duplicate ECGs and their paired originals were examined independently for determination of the intraobserver agreement of the manual scorer. The percentage of cases in which the manual scorer agreed with the observation from the paired ECG was assessed for each criterion. The level of intraobserver agreement attained in this analysis and the results of automation were compared to evaluate the efficacy of each method.

Development of automated application: The development of software for automated QRS scoring first required establishing precise definitions of the Selvester criteria to be incorporated into the program logic. This required repetitive interactions between the developer of the automated method and the manual scorer. These definitions were programmed in the C-language to generate the software capable of applying the Selvester criteria using a standard IBM/XT microcomputer. The automated QRS score was derived from the median beat complex[16] in each lead as constructed from a 10-second recording.

From the 438 ECGs scored by both manual and automated methods 100 were randomly selected as a learning subset to identify program errors in the software. This was facilitated by the creation of an "error identification" program that elucidated the precise nature of each disagreement (Figure 2). With this process, human errors could be easily identified and those automated versus manual results that remained dis-

Complete 54-Criteria, 32-Point QRS Scoring System*

Lead	Maximum Lead Points	Criteria	Points
I	(2)	Q≥30 ms	(1)
		R/Q ≤1	(1)
		R≤0.2 mV	(1)
II	(2)	Q≥40 ms	(2)
		Q≥30 ms	(1)
aVL	(2)	Q≥30 ms	(1)
		R/Q ≤1	(1)
aVF	(5)	Q≥50 ms	(3)
		Q≥40 ms	(2)
		Q≥30 ms	(1)
		R/Q ≤1	(2)
		R/Q ≤2	(1)

V_1			
Anterior	(2)	Any Q	(1)
		Q or S≥1.8 mV	(1)
Posterior	(4)	R/S ≥1	(1)
		R≥50 ms	(2)
		R≥1.0 mV	(2)
		R≥40 ms	(1)
		R≥0.6 mV	(1)
		Q and S≤0.3 mV	(1)

V_2			
Anterior	(1)	Any Q	(1)
		R≤10 ms	(1)
		R≤0.1 mV	(1)
		R≤R V_1 mV	(1)
Posterior	(4)	R/S ≥1.5	(1)
		R≥60 ms	(2)
		R≥2.0 mV	(2)
		R≥50 ms	(1)
		R≥1.5 mV	(1)
		Q and S≤0.4 mV	(1)

V_3	(1)	Any Q	(1)
		R≤20 ms	(1)
		R≤0.2 mV	(1)
V_4	(3)	Q≥20 ms	(1)
		R/S ≤0.5	(2)
		R/Q ≤0.5	(2)
		R/S ≤1	(1)
		R/Q ≤1	(1)
		R≤0.7 mV	(1)
		Notched R	(1)
V_5	(3)	Q≥30 ms	(1)
		R/S ≤1	(2)
		R/Q ≤1	(2)
		R/S ≤2	(1)
		R/Q ≤2	(1)
		R≤0.7 mV	(1)
		Notched R	(1)
V_6	(3)	Q≥30 ms	(1)
		R/S ≤1	(2)
		R/Q ≤1	(2)
		R/S ≤3	(1)
		R/Q ≤3	(1)
		R≤0.6 mV	(1)
		Notched R	(1)

*When more than one criterion in the brace is met, select the one with the most points. Notched R indicates a notch that begins within the first 40 ms.

FIGURE 1. The Selvester QRS scoring system, consisting of 54 criteria for a total of 32 points. Each point represents approximately 3% infarction of the left ventricle. Note that there are 12 unique criteria, with the remaining 42 contained in bracketed groups arranged by decreasing weights. Reproduced with permission from Hindman et al, Am J Cardiol.[6]

cordant were considered to be due to inadequate criteria definitions or faulty program logic. The program was then revised accordingly and retested in the same learning set. This developmental process was repeated until all errors of the automated method that could have been caused by inadequacy of definition or logic had been eliminated. Errors persisting beyond this point were attributed to the limitations intrinsic to automation. The resultant software was considered to be "automated Selvester QRS scoring" and was used in all the subsequent analyses.

Validation of automated Selvester QRS scoring: As outlined by Hindman et al,[6] precise application of the Selvester QRS scoring system requires defining the aspects of the waveforms rigorously, weighting the criteria to award additional points when there are increasing magnitudes of the same waveform abnormality, and selecting appropriate criteria within a group. It is important to note that because there are only 12 unique criteria, and the remaining 42 are contained within groups (Figure 1), it was possible for the automated and manual methods to achieve the same score through selection of different criteria (Figure 2). Thus, it was essential that the ECGs be compared by each individual criterion as well as by total score. This extensive validation procedure was necessary to identify the errors intrinsic to automation and to categorize the errors of manual application.

```
                                116210000     12/19/82    18:09
Age: 65  Sex: M  Cath Date: 12/20/82  EF: 59  Wall Motion: 3111113 (FFH)

<<<< C o m p u t e r   S c o r e >>>>

--*- II  Qdur >= 30
--*- aVF Qdur >= 30
--*- aVF Qdur >= 40
--*- aVF Qdur >= 50
--*- aVF R/Q <= 2
--*- aVF R/Q <= 1
--*- V1  Any Q
--*- V2  Any Q
     V2  Ramp <= 100
     V2  Rdur <= 10
     V2  Ramp V2 <= V1

     Computer Duke Score = 8

<<<<  M a n u a l  S c o r e  >>>>

--*- aVF Qdur >= 30
--*- aVF Qdur >= 40
--*- aVF Qdur >= 50
--*- aVF R/Q <= 2
--*- aVF R/Q <= 1
--*- V1  Any Q
--*- V2  Any Q
     V2  Ramp <= 100
     V2  Rdur <= 10
     V2  Ramp V2 <= V1
--*- V3  Rdur <= 20
     V3  Ramp <= 200

     Manual  Duke  Score = 8


<<<< Computer Criteria NOT Noted in Manual Score >>>>

--*- II  Qdur >= 30


<<<< Manual Criteria NOT Noted in Computer Score >>>>

--*- V3  Rdur <= 20
     V3  Ramp <= 200
```

FIGURE 2. Error identification between manual and automated scoring was facilitated by an automated comparison of criteria selected by each method. Criteria listed were determined to be present by the respective methods. Criteria marked --*- indicate 1 point awarded. Refer to Figure 1 for determination of the weighting of criteria contained within groups. It is important to note that a score of 8 was achieved by both the computer and the manual scorer through selection of different criteria, thus emphasizing the need to evaluate the electrocardiograms criterion by criterion.

Results

The distributions of automated and manual scores are shown in Figure 3. Manual scores ranged from 0 to 15, with a mean of 2.85 ± 3.17 points. The automated

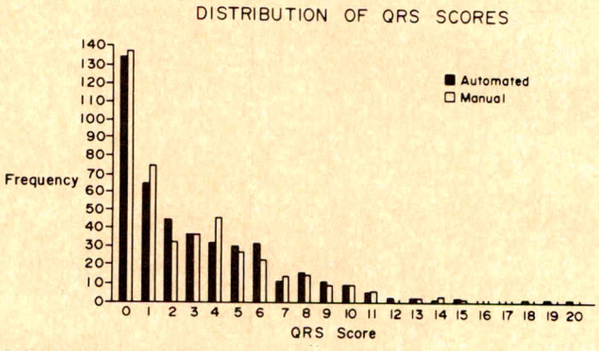

FIGURE 3. Comparison between the distributions of automated and manual QRS points for the 438 electrocardiograms. Automated scores ranged from 0 to 20. Manual scores ranged from 0 to 15.

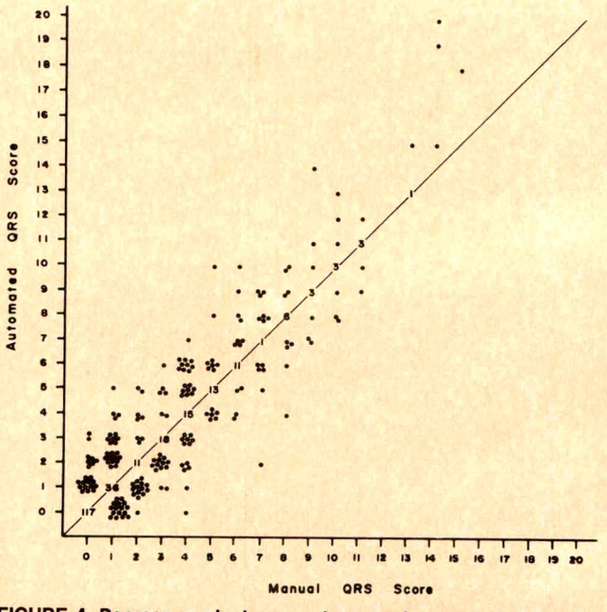

FIGURE 4. Pearson product-moment regression analysis between automated and manual Selvester QRS scores yielded a correlation coefficient of 0.94. The line of identity with the corresponding identical score matches (in numerals) are shown.

scores ranged from 0 to 20, with a mean of 3.05 ± 3.46 points. The 2 methods were significantly different from each other, with p = 0.0003 by the signal rank test. The average difference between methods was −0.2032 ± 1.2167 points, with a median of 0 (range −6 to 5 points). While Pearson product-moment regression analysis revealed a correlation coefficient of 0.94, only 54% (n = 238) of the ECGs matched overall scores identically (Figure 4). The average difference in score for the remaining 200 ECGs was −0.445 ± 1.7728 points, with a median of −1 (range −6 to 5 points).

Errors intrinsic to automation included failure to recognize minute R and S waves <20 mV and failure to detect downstroke R-wave notching. Errors in manual application were due to data recording and arithmetic, mismeasurement of waveforms, failure to accurately assess the isoelectric periods, criteria oversights and beat-to-beat variations of the waveforms.

Intraobserver agreement for the paired sets of duplicate ECGs revealed that the manual scorer matched criteria selection identically in only 60 of the 93 sets (65%). There were other instances in which the total score matched but the criteria selection did not, as illustrated by the example in Figure 2. Each of the 54 criteria when examined independently had agreement levels ranging from 96% to 100%.

The time required to score the 438 ECGs of the primary data set plus the 93 duplicate ECGs (total 531) by the automated method using an IBM/XT microcomputer was 1% of the time required for manual scoring of the same ECGs (20 minutes vs 36 hours, respectively).

Discussion

With the advent of interventional techniques aimed at limiting acute MI size, such as thrombolytic therapy and coronary angioplasty, the availability of indexes that can estimate the amount of myocardium in jeopardy, the extent of final MI and the prognosis have great importance. The standard 12-lead ECG is being examined for an increased role in this clinical setting because it is readily available and can be performed quickly at low cost.[7–14] The present study offers enhancement of an existing method for estimation of MI size, the Selvester QRS scoring system. While the practical limitations inherent to manual application of this method—such as time, training, variability and bias—have made it difficult for the Selvester system to gain wide recognition, an automated version would likely augment its usefulness in the routine assessment of the MI patient. Indeed, the relatively low level of intraobserver agreement of even the expert manual scorer (65%) supports the need for automation to provide a reliable, expeditious method that can quickly and reproducibly estimate MI size in an individual patient or in large research populations.

Although there are problems with manual application, conversion to an automated system also has limitations. Other attempts to automate the Selvester system have had suboptimal results, limited primarily by the lack of sufficient on-going intensive interactions between the manual scorer and the software developer to establish criteria definitions.[17,18] Because precise definitions of criteria include literal applications as well as the nuances of manual interpretation, the translation process from human to computer is extremely difficult. Although the algorithms may appear well described, intricate waveforms occur that make application of certain criteria ambiguous. While a trained observer can intelligently modify his or her approach in these cases, a computer is limited unless this logic has been fully considered and incorporated into the program. Because it is not possible to consider all intricacies of a waveform there will always be instances where the observer's knowledge about electrocardiography will result in an educated opinion for the correct application of a particular criterion. However, this same knowledge of ECG interpretation leads to bias in the scoring process. Although computerization of complex, but systematic, logic can assist clinical decision-making, it must also be recognized that as the number and complexity of the programmed criteria increase, the clinicans using the system will tend to have less knowledge of the criteria incorporated into the program logic. This may lead to overreliance or false confidence in computer results when complex scoring systems are used.

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Significance of Q-Wave Regression After Transmural Acute Myocardial Infarction

SANTIAGO COLL, MD, AMADEO BETRIU, MD, TOMÁS DE FLORES, MD, EULALIA ROIG, MD, GINÉS SANZ, MD, LUIS MONT, MD, JORGE MAGRIÑÁ, MD, ANTONIO SERRA, MD, and FRANCISCO NAVARRO LÓPEZ, MD

A total of 313 consecutive patients was studied to assess the prevalence and prognostic implications of Q-wave loss after transmural acute myocardial infarction. Heart catheterization, including single-plane left ventriculography and selective coronary arteriography, was performed before hospital discharge. After a mean follow-up of 65 (1 to 100) months, 34 patients (11%) lost their Q waves. The time interval from the acute event to the first electrocardiogram showing Q-wave disappearance was 14 (1 to 32) months. Peak creatine kinase value was significantly higher in patients who retained their Q waves than in those who lost them (1,121 ± 813 vs 779 ± 464 IU, respectively, $p < 0.05$). Severity of coronary artery disease, as judged by the number of diseased arteries and the number of arteries with total or subtotal occlusion, was similar in both groups. However, patients showing Q-wave regression had lower left ventricular end-diastolic pressure, higher ejection fraction and fewer abnormally contracting segments than their counterparts (12 ± 6 vs 15 ± 7 mm Hg, $p < 0.05$; 53 ± 11 vs 44 ± 14%, $p < 0.001$; 1 ± 1 vs 2 ± 1 segments, $p < 0.001$, respectively). In addition, no patient with normalized electrocardiogram presented with left ventricular aneurysm. Although differences in mortality, nonfatal reinfarction and new onset of angina between the 2 groups were not significant, congestive heart failure was prevalent among patients with permanent Q waves (23 vs 6%, $p < 0.05$). Our findings suggest that Q-wave loss after AMI may be related to a smaller infarct size.

(Am J Cardiol 1988;61:739–742)

It has recently been recognized that loss of Q waves after transmural acute myocardial infarction [AMI] is not as unusual as previously suspected.[1-3] However, conflicting results have been published with regard to the prevalence and prognostic implications of Q-wave regression following AMI. Discrepancies among series are to be expected because available studies deal with selected groups of patients and lack angiographic data. The present investigation assesses the natural history of patients with transmural AMI in whom serial electrocardiograms showed disappearance of diagnostic Q waves.

From the Cardiovascular Unit, Hospital Clínico, University of Barcelona, Barcelona, Spain. Manuscript received July 27, 1987; revised manuscript received November 17, 1987, and accepted November 22.

Address for reprints: Amadeo Betriu, MD, Coronary Unit, Hospital Clínico, Casanova 143, Barcelona 08036, Spain.

Methods

Patients: From January 1975 to January 1980, 376 men with AMI aged ≤60 years were admitted to our institution. A detailed description of the University of Barcelona's Myocardial Infarction Project has been published elsewhere.[4] Of 357 survivors, 44 were excluded from the study due to either coexisting noncardiac life-threatening conditions (5 patients), refusal to undergo coronary angiography (24) or to the presence of non-Q-wave AMIs (15). Thirty four of the remaining 313 patients showed regression of Q waves on serial electrocardiograms and formed the basis of this study.

Criteria for infarction: Myocardial infarction was diagnosed when evolving Q-wave abnormalities with ST-segment and T-wave changes were associated with either ischemic chest pain lasting >20 minutes or serial elevation of serum enzymes. Previous infarction was diagnosed when either prior hospital admission for documented AMI or electrocardiographic Q-wave abnormalities diagnostic of an old infarction was present.

Transmural myocardial infarction was coded according to location as anterior, inferior or combined. Criteria for infarction was based on major (Minnesota Code 1,1), moderate (1,2) or minor (1,3) electrocardiographic findings, as determined by the duration and depth of Q waves and the leads in which they appear.[5]

Catheterization and angiographic procedures: Heart catheterization was performed within 1 month of the acute event. Left ventriculograpjy was carried out in the 30° right anterior oblique projection. Coronary arteriograms were obtained in multiple projections. Left ventricular volumes and ejection fraction were determined using the area-length method.[6] To assess regional wall motion, 5 areas of interest were considered: anterobasal, anterolateral, apical, diaphragmatic and posterobasal.[7] The systolic change for each region was measured as the segmental ejection fraction. Lesions of <50% reduction in diameter were considered to be nonobstructive. Total coronary occlusion was defined as the absence of forward flow of contrast material in the involved artery. Each patient was classified as having 1-, 2- or 3-vessel disease. Obstructions of diagonal and marginal branches were considered lesions of the left anterior descending or circumflex artery, respectively. Collaterals were judged to be well developed when the diameter of the receiving artery measured >1 mm and the sending vessel showed no obstructive lesions.

Follow-up: Patients were seen monthly during the first 3 months and every 3 months thereafter. Clinical status, results of physical examination and a 12-lead electrocardiogram were recorded at each visit. Mean follow-up was 65 months (1 to 100).

Statistical analysis: Differences between patients who retained their Q waves and those who lost them were analyzed using the Statistical Package for Social Sciences,[8] applying the Student *t* test, Fischer exact test or the chi-square test, when appropriate. Survival analysis was done by constructing Kaplan-Meier actuarial curves for the 2 groups.[9] Statistical differences were assessed by the log-rank test.[10] A p value <0.05 was considered significant.

TABLE I Clinical and Angiographic Data

	Q Wave Lost	Q Wave Retained	p Value
No.	34	279	
Mean age (yr)	48 ± 8	51 ± 7	
Previous AMI (%)	1 (3)	30 (10)	NS
Previous angina (%)	14 (41)	136 (48)	NS
Systemic hypertension (%)	12 (35)	107 (38)	NS
Diabetes mellitus (%)	7 (20)	55 (19)	NS
Dyslipemia (%)	19 (56)	97 (34)	NS
Cigarette smoking (%)	32 (94)	17 (92)	NS
Creatine kinase	779 ± 464	1,121 ± 813	<0.02
LVEDP (mm Hg)	12 ± 6	15 ± 7	<0.03
Ejection fraction (%)	53 ± 11	44 ± 14	<0.0003
Affected areas	1 ± 1	2 ± 1	<0.00001
LV aneurysm (%)	0	42 (15)	<0.02
Coronary arteries narrowed >50% in diameter			
0 (%)	3 (9)	16 (6)	NS
1 (%)	15 (44)	93 (33)	NS
2 (%)	8 (23.5)	94 (33)	NS
3 (%)	8 (23.5)	79 (28)	NS
Coronary collaterals (%)	2 (6)	38 (13)	NS

AMI = acute myocardial infarction; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; NS = not significant.

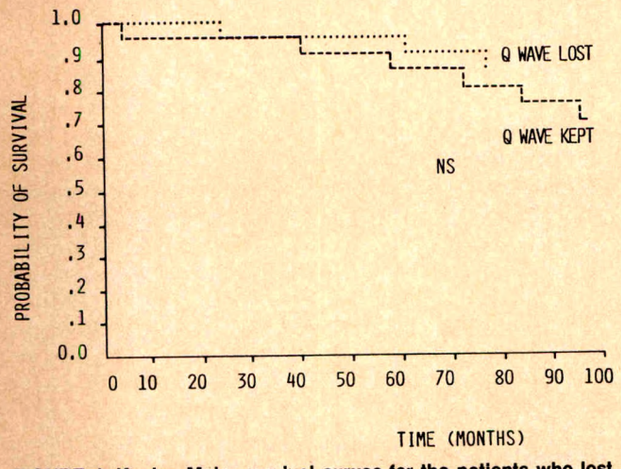

FIGURE 1. Kaplan-Meier survival curves for the patients who lost their Q waves and those who kept them. No differences were found when both populations were compared (85% and 75% survival at 7.5 years, respectively).

Results

Prevalence: Loss of Q waves was documented in 34 patients (11%). The time interval from the AMI to the first electrocardiogram showing Q-wave disappearance was 14 ± 10 months (mean ± standard deviation, range 1 to 32). Loss occurred in 53% of patients with anterior and 44% of patients with inferior AMI. Q loss occurred 3% of the time when the infarction involved both anterior and inferior walls.

Clinical and angiographic findings: Baseline clinical data and catheterization findings are listed in Table I. Patients who lost Q waves had a lower peak creatine kinase level (779 ± 464 vs 1,121 ± 813 IU, p <0.05) than their counterparts. Age, previous history of coronary artery disease, hypertension, dyslipemia, cigarette smoking and diabetes mellitus were not different in the 2 groups. Left ventricular end-diastolic pressure was lower (12 ± 6 vs 15 ± 7 mm Hg, p <0.05) and ejection fraction higher (53 ± 11 vs 44 ± 14%, p <0.001) in patients who lost their Q waves. Regional wall motion analysis showed that this group of patients had fewer abnormally contracting segments (1 ± 1 vs 2 ± 1 segments, p <0.0001) and higher prevalence of normal left ventricular angiograms (35 vs 12%, p <0.001) than those who retained Q waves. In addition, no patient with a normalized electrocardiogram had left ventricular aneurysm (p <0.05). The number of diseased arteries and the number of arteries showing total or subtotal (>90%) lesions was comparable in both groups of

patients. Similarly, no differences were found between the 2 groups with regard to the presence of well developed collaterals.

Follow-up: Fifty-two patients, 4 who lost and 48 who kept their Q waves, died during the follow-up period. Figure 1 shows the Kaplan-Meier actuarial curves for the 2 groups. No differences were found when both populations were compared (75 and 85% survival rates at 7.5 years, respectively). Prevalence of nonfatal reinfarction (3 vs 34 patients) and new onset angina (18 vs 150) was similar in both groups. Congestive heart failure, however, was more frequently found among patients with permanent Q waves (2 vs 63, $p < 0.05$).

Discussion

Prevalence: Retrospective studies[1,2] have found the prevalence of Q-wave regression after AMI to vary between 7 and 15%. To our knowledge, the present investigation represents the first attempt to assess the prevalence of Q-wave loss in a series of unselected consecutive patients surviving an AMI. Thus, the finding that 34 of 313 AMI survivors (11%) lost their Q waves after a mean time interval of 14 ± 10 months is relevant because the study population included 91% of potential candidates and follow-up was complete in all but 13 patients. Although we analyzed a limited age group of men, this series included 70% of all patients with AMI admitted in our unit. Thus, our results are not likely to be biased by selection criteria. In the Aspirin Myocardial Infarction Study[3] (AMIS), 14% of the patients lost Q waves that were present on the qualifying electrocardiogram. Differences between that trial and our own series are minor and might be related to patient selection criteria, as participants in the AMIS trial were older than our cohort and entered the study at variable time intervals after the acute event. In addition, unstable patients and early deaths (within 2 months after myocardial infarction) were excluded from the AMIS protocol.

Clinical and angiographic findings: Previous reports of patients who lost Q waves after AMI do not include angiographic data.[1,3] The present study showed the prevalence of total or subtotal occlusion of the involved artery to be comparable in patients who lost their Q waves and those who retained them. Nevertheless, the latter group had a better left ventricular function, as substantiated by a higher ejection fraction, fewer abnormally contracting segments and lower left ventricular end-diastolic pressure. These data, plus the finding of a lower peak creatine kinase value, strongly suggest a smaller infarct size in patients with lost Q waves. Of interest in that regard is the recent documentation of a negative relation between infarct size (as assessed by an electrocardiographic score) and left ventricular ejection fraction.[11,12]

Q-wave regression mechanism: A review of clinical and angiographic data was of little help in identifying the exact mechanism of Q-wave regression in our series. It is known that a new ventricular conduction disturbance may alter activation pathways and mask prior Q waves. Similarly, a second myocardial infarction involving the contralateral ventricular wall may cause an apparent regrowth of R waves over the area of previous infarct.[13] In our case, however, these 2 mechanisms are unlikely as demonstrated by serial electrocardiogram readings of individual patients and, in the case of reinfarction, by lack of clinical manifestations. The disappearance of Q waves has been documented after successful myocardial revascularization[14]; similarly, increased local flow by late coronary artery recanalization[15-17] might well explain the Q-wave loss in our series. However, this hypothesis cannot be proven because repeat angiography was not performed. Alternatively, regression of Q wave may result from progressive reduction of scar tissue to a critical-size area.[18]

Prognostic implications: After reviewing serial electrocardiograms from 251 men, Kaplan and Berkson[2] failed to find any difference in survival between patients whose Q waves disappeared (21%) and those whose Q waves persisted (30%). Kalbfleisch et al[1] analyzed a series of 775 patients with myocardial infarction, 52 of whom (7%) showed complete disappearance of diagnostic Q waves. The mortality rate of this subset was comparable to that of the entire group (21 vs 23%). Data from the Coronary Drug Project[19] conflicted with these observations because infarct survivors with Q patterns on the baseline electrocardiogram had a >3-fold mortality of those with no residual recordable Q waves after infarction (13 vs 4%, $p < 0.01$). The reason for the discrepancy between the Coronary Drug Project and earlier series may be that the latter study specifically referred to loss of Q waves whereas the former referred only to the fact that there was no Q wave present at baseline. In the AMIS cohort,[3] the mortality associated with the absence or loss of Q waves did not differ from that in patients who had a single infarct and persistent Q waves. However, patients with extensive areas of infarction, as indicated by multiple infarct sites or major coding criteria, had a significantly higher total mortality than patients who lost Q waves. In keeping with these findings we showed by actuarial analysis that the mortality rate after Q-wave regression was comparable to that of patients with permanent Q waves.

The lack of significant differences in the rates of reinfarction and angina between patients who lost their Q waves and those who kept them probably is related to the extent and severity of coronary artery lesions found to be comparable in both groups. The prevalence of congestive heart failure among patients with permanent Q waves is in agreement with the higher left ventricular end-diastolic pressure and rate of left ventricular aneurysms in this group.

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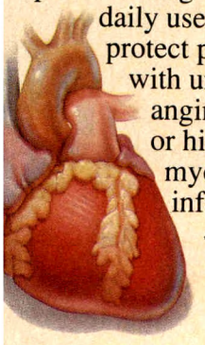

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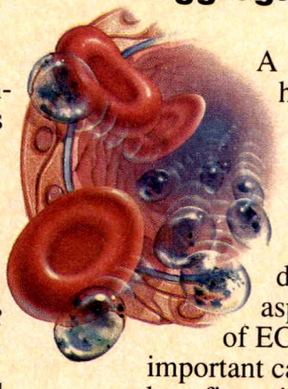
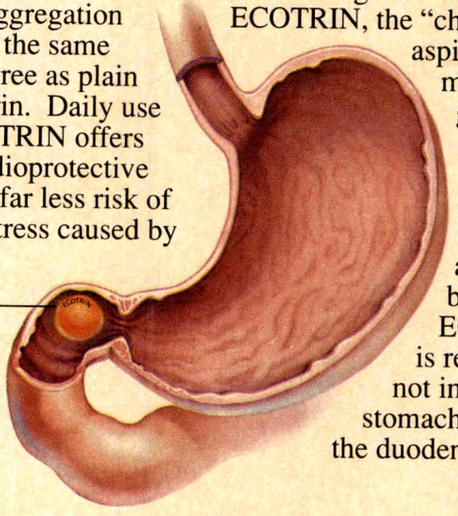


A recent study[2] has shown that ECOTRIN inhibits platelet aggregation to the same degree as plain aspirin. Daily use of ECOTRIN offers important cardioprotective benefits–with far less risk of the gastric distress caused by plain aspirin.

Enteric-coated to spare the stomach.

More than 1,000 endoscopies have proved ECOTRIN superior to plain, buffered, and highly buffered aspirin in protecting the stomach in a regimen of 4 g a day.[3] ECOTRIN, the "chronic-use" aspirin, minimizes the gastric damage often associated with other forms of aspirin because ECOTRIN is released not in the stomach but in the duodenum.



ECOTRIN is released not in the stomach but in the duodenum.

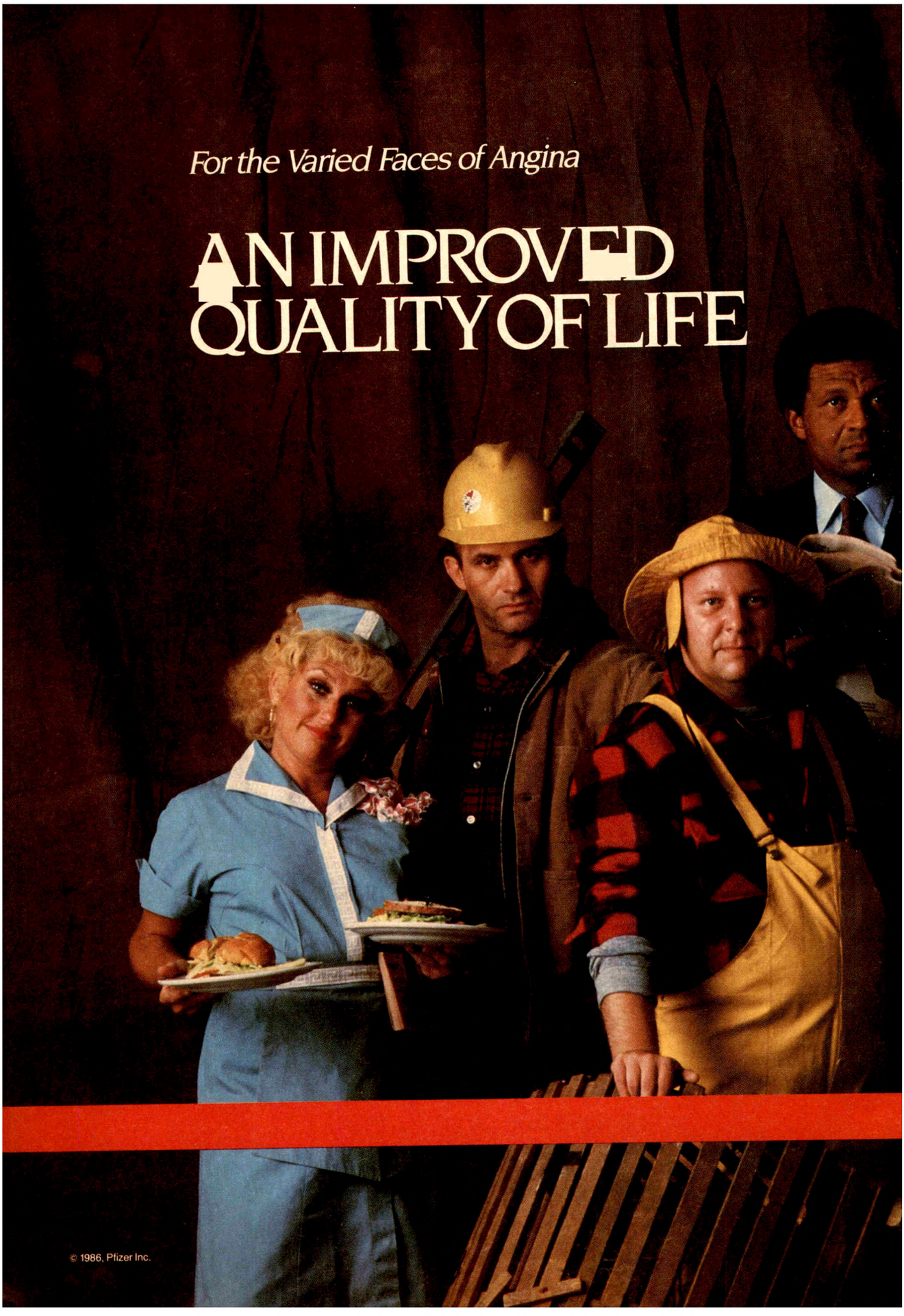
Targeted-Release
Ecotrin®
Safety-Coated Aspirin 325 mg and 500 mg Tablets

The cardioprotective stomach-sparing aspirin.

SmithKline Consumer Products
A SMITHKLINE BECKMAN COMPANY

JAM-2071

References: 1. National audit of physician practices; data on file, SmithKline Consumer Products, a SmithKline Beckman Company. **2.** Faigel DJ, Jakubowski JA, Stampfer MJ, et al: Multiple doses of regular and enteric-coated aspirin produce equivalent platelet inhibitory effects. *Curr Ther Res* 1986; 39:519-527. **3.** Data on file, SmithKline Consumer Products, a SmithKline Beckman Company.


For the Varied Faces of Angina
AN IMPROVED QUALITY OF LIFE
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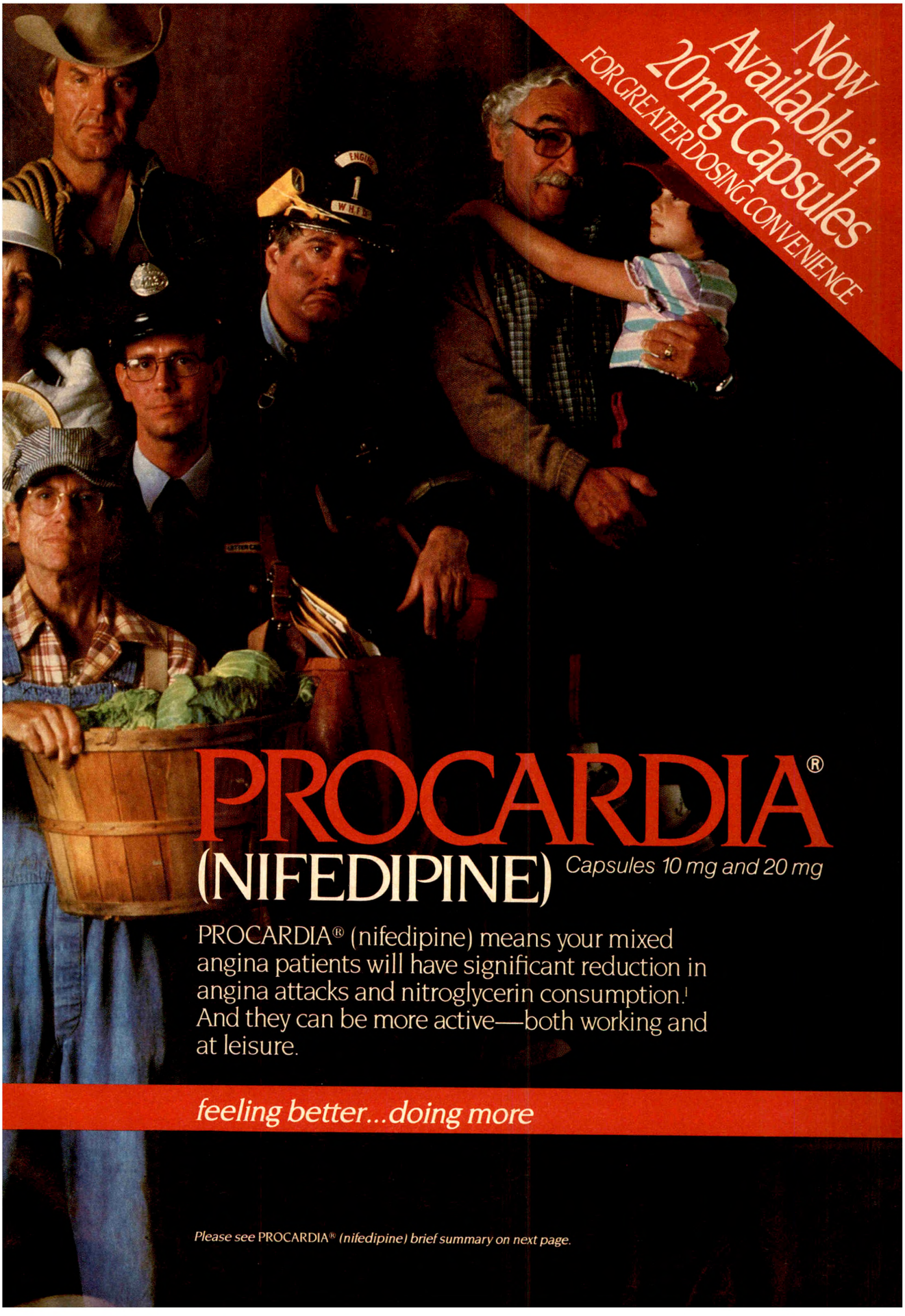
Now Available in 20mg Capsules
FOR GREATER DOSING CONVENIENCE
PROCARDIA®
(NIFEDIPINE)
Capsules 10 mg and 20 mg
PROCARDIA® (nifedipine) means your mixed angina patients will have significant reduction in angina attacks and nitroglycerin consumption.[1] And they can be more active—both working and at leisure.
feeling better...doing more
Please see PROCARDIA® (nifedipine) brief summary on next page.

feeling better...doing more

PROCARDIA®
(NIFEDIPINE)

Capsules 10 mg and 20 mg

–Effective dosage range is 30-120 mg/day

For most patients, start with 10 mg *t.i.d.*, and titrate over 7 to 14 days, using the patient's blood pressure response, attack frequency, sublingual nitroglycerin intake and activity level as a guide. Titration may be more rapid (e.g., 3 days) if symptoms warrant and the patient is observed closely.

Because PROCARDIA decreases peripheral vascular resistance (occasional patients have had excessive hypotension), careful monitoring of blood pressure during initial administration and upward dosage titration is suggested, especially for patients taking other drugs known to lower blood pressure. Occasional patients have developed increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases.

–Offers a favorable safety profile

Most frequently reported side effects associated with PROCARDIA therapy, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients; transient hypotension in about 5%; palpitation in about 2%; syncope in about 0.5%.

Reference:
1. Stone PH, Muller JE, Turi ZG, et al: Efficacy of nifedipine therapy in patients with refractory angina pectoris: Significance of the presence of coronary vasospasm. *Am Heart J* 1983; 106:644-652.

Brief Summary For Oral U
PROCARDIA® (nifedipine) Capsules

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the manag ment of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest a companied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the pr ence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, p vided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentati suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain l a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible w intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the mana ment of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who rem symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmatio sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-block agents may be beneficial in patients with chronic stable angina, but available information is not sufficien predict with confidence the effects of concurrent treatment, especially in patients with compromised left v tricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care m be taken to monitor blood pressure closely since severe hypotension can occur from the combined effect the drugs. (See WARNINGS.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDI modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These sponses have usually occurred during initial titration or at the time of subsequent upward dosage adjustm and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiv PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using h dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combinatio PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low dose fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCAR treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician shoul aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 ho should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe structive coronary artery disease, have developed well documented increased frequency, duration and/or verity of angina or acute myocardial infarction on starting PROCARDIA or at the time of dosage increase. mechanism of this effect is not established.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal drome with increased angina, probably related to increased sensitivity to catecholamines. Initiatio PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provol reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blo withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stop them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resista careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is sugges Close observation is especially recommended for patients already taking medications that are known to l blood pressure. (See WARNINGS.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This ed occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose an is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema fron effects of increasing left ventricular dysfunction.

Laboratory tests: Rare, usually transient, but occasionally significant elevations of enzymes such as line phosphatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to PROCARDIA therapy i certain in most cases, but probable in some. These laboratory abnormalities have rarely been associated clinical symptoms, however, cholestasis with or without jaundice has been reported. Rare instances of all hepatitis have been reported.

Limited clinical studies have demonstrated a moderate but statistically significant decrease in platele gregation and increase in bleeding time in some PROCARDIA (nifedipine) patients. No clinical significanc these findings has been demonstrated. Positive direct Coombs test with/without hemolytic anemia has reported.

Although PROCARDIA has been used safely in patients with renal dysfunction and has been reported to a beneficial effect in certain cases, rare, reversible elevations in BUN and serum creatinine have been repo in patients with pre-existing chronic renal insufficiency. The relationship to PROCARDIA therapy is uncerta most cases but probable in some.

Drug interactions: Beta-adrenergic blocking agents: (See INDICATIONS AND WARNINGS.) Experien over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports sugge that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerb of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no trolled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal unteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thi patients with coronary artery disease. In an uncontrolled study of over two hundred patients with conge heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin l be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or u digitalization.

Coumarin anticoagulants: There have been rare reports of increased prothrombin time in patients taking marin anticoagulants to whom PROCARDIA was administered.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasm els (80%) and area-under-the-curve (74%) after a one week course of cimetidine at 1000 mg per day and ipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. If nifedipine therapy is ini in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to ra two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused red fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity st were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats and embryoto rats, mice and rabbits. There are no adequate and well controlled studies in pregnant women. PROCA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: The most common adverse events include dizziness or lightheadedness, perip edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hyp sion in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recu reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, shortness of breath, rhea, constipation, gastrointestinal cramps, flatulence, inflammation, joint stiffness, shakiness, jitteri sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, sexual difficulties, thrombocytopenia, anemia, leukopenia, purpura, allergic hepatitis, gingival hyperp depression, paranoid syndrome, transient blindness at the peak of plasma level, erythromelalgia, and ar with ANA (+). Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural h of the disease in these patients. It remains possible, however, that some or many of these events were related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulm edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0. patients.

HOW SUPPLIED: PROCARDIA soft gelatin capsules are supplied in:
Bottles of 100: 10 mg (NDC 0069-2600-66) orange #260; 20 mg (NDC 0069-2610-66) orange and light #261. Bottles of 300: 10 mg (NDC 0069-2600-72) orange #260; 20 mg (NDC 0069-2610-72) orange an brown #261. Unit dose packages of 100: 10 mg (NDC 0069-2600-41) orange #260; 20 mg (NDC 0069- 41) orange and light brown #261.

The capsules should be protected from light and moisture and stored at controlled room temperature 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request. Revised June 1986 © 1982, Pfiz

Pfizer **LABORATORIES DIVISION**
PFIZER INC.

LOWER HIS BLOOD PRESSURE

NOT HIS PERFORMANCE

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

START HIS DAY OUT RIGHT
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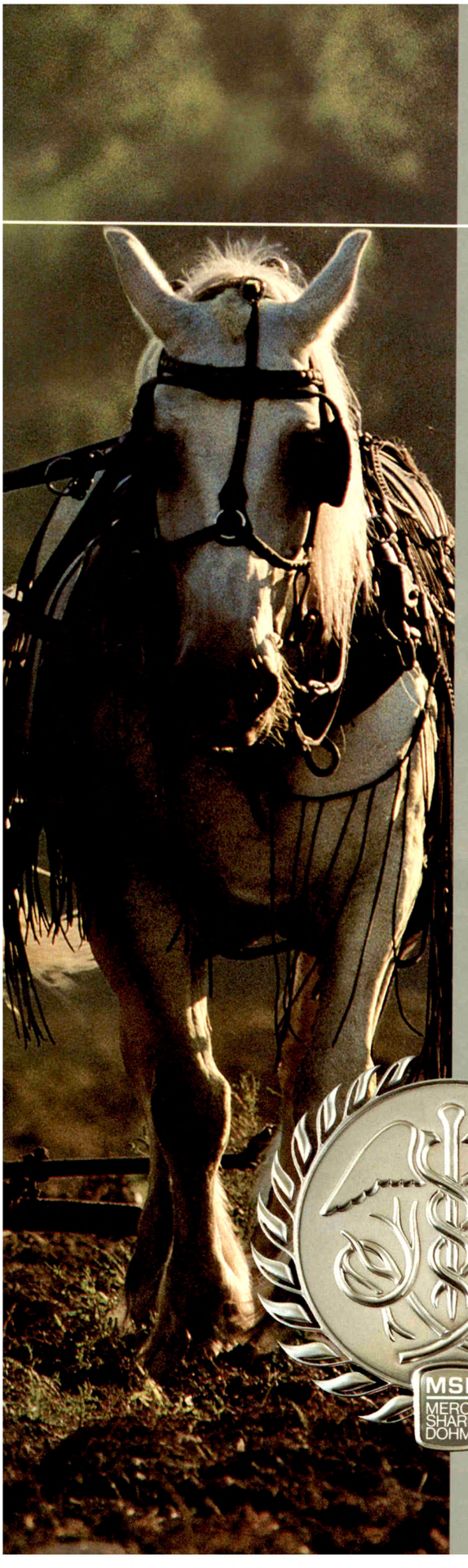

FOR MANY HYPERTENSIVE PATIENTS

Start with Once-a-Day

VASOTEC®

(ENALAPRIL MALEATE | MSD)

Certain CNS effects, such as impairment of memory, nightmares, or depression, have not been characteristic of VASOTEC.

Little or No Interference with Physical or Mental Activity

Certain subjective symptoms such as malaise and drowsiness, which may interfere with physical or mental activity, have not been characteristic of VASOTEC—a fact that may be related to the specificity of action of VASOTEC on the renin-angiotensin-aldosterone system.

VASOTEC is contraindicated in patients who are hypersensitive to this product.

Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with angiotensin-converting-enzyme (ACE) inhibitors, including VASOTEC (0.2% of patients treated with VASOTEC in clinical trials). In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.**

Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. In using VASOTEC, consideration should be given to the fact that another ACE inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and the available data are insufficient to show that VASOTEC does not have a similar risk.

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

MSD
MERCK SHARP & DOHME

It May Change the Way Your Patients Feel on Antihypertensive Therapy

VASOTEC®

(ENALAPRIL MALEATE | MSD)

Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Neutropenia/Agranulocytosis: Another ACE inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General: Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of VASOTEC and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION in complete Prescribing Information.)

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions.*)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least one hour after the initial dose. (See WARNINGS and DOSAGE AND ADMINISTRATION in complete Prescribing Information.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC® (Enalapril Maleate, MSD) may attenuate potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

There are no adequate and well-controlled studies in pregnant women. VASOTEC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2677 patients.

The most frequent clinical adverse experiences in controlled trials were: headache (4.8%), dizziness (4.6%), and fatigue (2.8%). For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences was not related to total daily dosage within the range of 10 to 40 mg. The overall percentage of patients treated with VASOTEC reporting adverse experiences was comparable to placebo.

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.6%), rash (1.5%), hypotension (1.4%), cough (1.3%), nausea (1.3%), and orthostatic effects (1.3%).

Clinical adverse experiences occurring since the drug was marketed or in 0.5 to 1.0% of patients in the controlled trials are listed below and, within each category, are in order of decreasing severity.

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); syncope; orthostatic hypotension; palpitations; chest pain.

Gastrointestinal System: Ileus, pancreatitis, hepatitis or cholestatic jaundice, abdominal pain, vomiting, dyspepsia, constipation.

Nervous System/Psychiatric: Depression, confusion, somnolence, insomnia, nervousness, paresthesia.

Renal: Renal failure, oliguria, renal dysfunction. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

Respiratory: Bronchospasm, dyspnea, rhinorrhea.

Other: Muscle cramps, hyperhidrosis, impotence, pruritus, asthenia, photosensitivity, alopecia, flushing, taste alteration, tinnitus, glossitis.

A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: Combining the results of clinical trials in patients with hypertension or congestive heart failure, hypotension (including postural hypotension and other orthostatic effects) was reported in 2.3% of patients following the initial dose of enalapril or during extended therapy. In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.)

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg (break the 5-mg tablet) should be used under medical supervision for at least one hour to determine whether excess hypotension will occur. (See WARNINGS and PRECAUTIONS, *Drug Interactions.)*

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance >30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤30 mL/min (serum creatinine ≥3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily. For dialysis patients, the initial dose and the dose on dialysis days is 2.5 mg/day. Dosage on nondialysis days should be adjusted depending on blood pressure response.

For more detailed information, consult your MSD representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

J7VS27(410)

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Limitations in the Interpretation of Rest-Exercise Ejection Fraction Changes After Early Thrombolytic Therapy During Acute Myocardial Infarction

FLORENCE H. SHEEHAN, MD, DETLEF G. MATHEY, MD, JOACHIM SCHOFER, MD, SUZANNE MITTEN, and EDWARD L. BOLSON, MS

The effect of exercise on left ventricular wall motion in the infarct and noninfarct regions, and their contribution to the global ejection fraction response to exercise was evaluated in 24 patients studied at least 2 weeks following thrombolytic therapy for acute myocardial infarction. To achieve this goal, a nonstandard protocol was used: contrast ventriculography was performed at rest and immediately following 3 minutes of supine bicycle exercise at 50 watts. Wall motion in the infarct and noninfarct regions was measured using the centerline method. The global ejection fraction response to exercise correlated poorly with the exercise response of motion in the infarct region ($r = 0.38$). In 15 of the 24 patients, the function of the infarct and noninfarct regions changed in opposing directions, and in only 8 (53%) of these did the global ejection fraction response follow the exercise response of motion in the infarct region. The motion of the noninfarct region was the predominant influence on the ejection fraction response in the other 7 patients. Subgroup analysis revealed that the global ejection fraction response was more dependent on the response of motion in the anterior wall ($r = 0.71$, $p < 0.001$) than in the inferior wall ($r = 0.16$), regardless of infarct location. The regional wall motion response to exercise also better distinguished reperfused from nonreperfused patients than did the ejection fraction response. These results indicate that the global ejection fraction response to exercise may be an unreliable indicator of the functional status of the infarct region. The efficacy of thrombolytic therapy for acute myocardial infarction in salvaging myocardium is more accurately evaluated from the rest-exercise change in regional wall motion.

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Studies of the prognostic value of measuring the rest-exercise ejection fraction response in patients who have suffered a recent myocardial infarction have had contradictory results. Some studies have reported a higher predictive accuracy with the exercise response than with the resting ejection fraction,[1–3] whereas others reported that the resting ejection fraction better predicted survival.[4] One reason may be that the global ejection fraction is an insensitive parameter of function in the infarct region in the presence of compensatory hyperkinesis of the noninfarct region.[5] Such hyperkinesis is primarily associated with acute infarction, but may occur later.[5,6] As a result, the severity of residual regional dysfunction and ischemia in the infarct site may be underestimated if the global ejection fraction response is maintained normal by enhanced contraction in noninfarct regions. The present study was performed to measure the change in regional wall motion with exercise in both the infarct and noninfarct regions in post-thrombolysis patients and to correlate these with the global ejection fraction response to exercise.

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Address for reprints: Florence H. Sheehan, MD, University of Washington RG-22, Seattle, Washington 98195.

Methods

Patients: The study comprised 28 patients, admitted at University Hospital Eppendorf ≤3 hours after onset of acute myocardial infarction, who received intracoronary streptokinase as previously described.[5] They

were recalled 10 days to 2.6 years later for repeat cardiac catheterization and exercise contrast angiography. Twenty-eight (34%) of 83 patients treated consented to testing. Using the Judkins procedure, coronary arteriography was performed, followed by ventriculography in the 30° right anterior oblique projection. After a 15-minute wait to allow dissipation of the effect of contrast on ventricular function,[7] the patient was exercised at 50 watts for 3 minutes on a supine bicycle. Ventriculography was then repeated. None experienced complications from the exercise. Both the rest and the exercise ventriculograms were analyzable in 24 patients, whose data constitute the subject of the present report.

Ventriculographic analysis: The cine films were analyzed at the University of Washington. Chamber volume was determined using the area length method[8] and global ejection fraction was then calculated. Hypokinesis in the infarct site and hyperkinesis in the opposite wall were measured using the centerline method (Figure 1), as previously described.[9]

Statistical analysis: Patient groups were compared using the unpaired *t* test for continuous variables and chi-square analysis for dichotomous variables. Change between rest and exercise was evaluated using the paired *t* test. Regional and global function were correlated via multiple linear regression analysis. Discriminant analysis was used to determine which parameter of left ventricular function best distinguished reperfused from nonreperfused patients.[10]

Results

Patients: Participants in the rest-exercise study were similar to those who declined (Table I), except

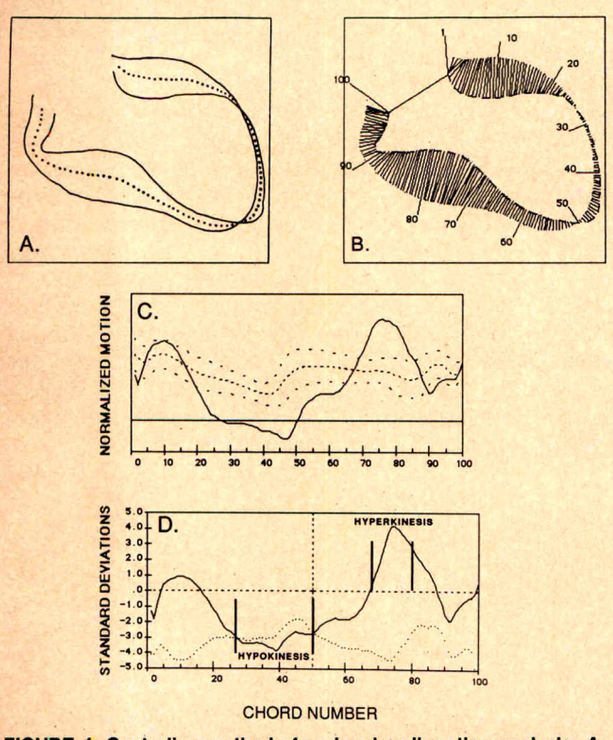

FIGURE 1. Centerline method of regional wall motion analysis. *A*, end-diastolic and end-systolic left ventricular endocardial contours and centerline constructed by the computer midway between the 2 contours. *B*, motion is measured along 100 chords constructed perpendicular to the centerline. *C*, motion at each chord is normalized by the end-diastolic perimeter to yield a shortening fraction. Motion along each chord is plotted for the patient (*solid line*). The mean motion in the normal ventriculogram group (*dashed line*) and 1 standard deviation above and below the mean (*dotted lines*) are shown for comparison. *D*, standardized motion. The wall motion of the patient is now plotted in units of standard deviations from the normal mean (*dotted line*). The normal ventriculogram group mean is represented by the horizontal zero-line. Vertical lines delimit the most hyperkinetic and most hypokinetic parts of the anterior and inferior regions.

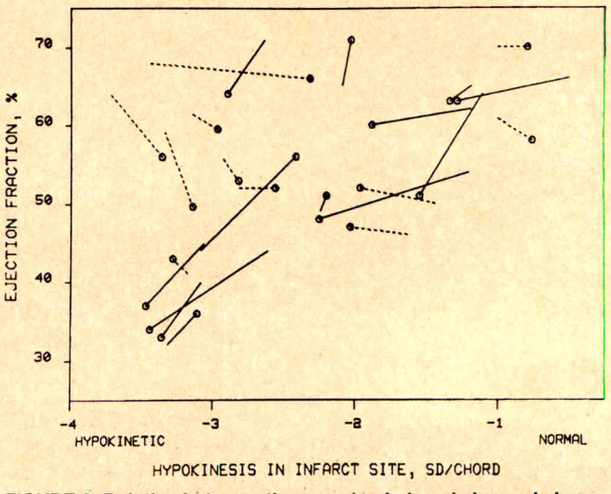

FIGURE 2. Relation between the exercise-induced change in hypokinesis in the infarct site and the change in ejection fraction. The rest study is indicated by the *circles*. *Solid lines* indicate concordance between the changes in regional and global function; *dashed lines* indicate discordance. SD = standard deviation.

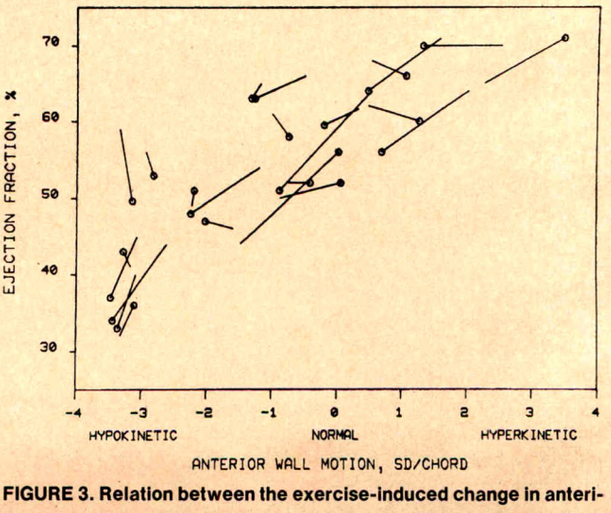

FIGURE 3. Relation between the exercise-induced change in anterior wall motion and the change in ejection fraction. SD = standard deviation.

TABLE I Comparison of Patients Who Did Versus Did Not Participate in the Rest-Exercise Protocol

	Participant	Nonparticipant	p Value
No.	24	59	
Age (yrs)	50 ± 9	54 ± 13	NS
Men (%)	92	80	NS
Infarct location (% anterior)	63	56	NS
1-vessel disease (%)	37	34	NS
Time to thrombolytic therapy (hr)	3.8 ± 3.4	3.1 ± 1.3	NS
Acute ejection fraction (%)	51 ± 10 (21)	54 ± 14	NS
Initial stenosis in infarct artery (%)	100 ± 0	99 ± 2	0.011
Residual stenosis in infarct artery (%)	84 ± 20	87 ± 14	NS
Reperfusion rate* (%)	75	75	NS
Peak creatine phosphokinase	1,314 ± 820 (19)	1,227 ± 1,119 (50)	NS
Return to work (%)	5 (20)	23 (44)	NS
1-year survival (%)	95 (22)	91 (56)	NS

Numbers within parentheses indicate number of patients if it is smaller than the total.
* Reperfusion defined as sustained infarct artery or graft patency (see text); NS = not significant.

TABLE II Rest-Exercise Change in Ventricular Function

	Rest	Exercise	p Value	Range of Change
Ejection fraction (%)	53 ± 11	55 ± 11	<0.05	−6 to +13
Wall motion, SD/chord				
Infarct site	−2.4 ± 0.8	−2.3 ± 1.0	NS	−1.1 to +1.1
Noninfarct site	0.5 ± 1.2	0.5 ± 1.2	NS	−1.5 to +1.9
End-diastolic volume (ml)	178 ± 67	196 ± 64	<0.001	−17 to +67
End-systolic volume (ml)	85 ± 36	88 ± 35	NS	−23 to +30
Stroke volume (ml)	93 ± 42	109 ± 44	<0.001	−24 to +49
Cardiac output (liter/min)	7.6 ± 3.4	11.1 ± 4.4	<0.001	−0.7 to +7.0
Heart rate (beats/min)	82 ± 15	103 ± 16	<0.001	−9 to +49

NS = not significant ($p \geq 0.05$); SD = standard deviations from the mean of the normal reference group.

that all study patients had total occlusion of the infarct artery before thrombolytic therapy. Eighteen patients were considered fully reperfused because the full length of the infarct artery was reperfused after streptokinase therapy, and either (1) the infarct artery was patent at follow-up and there was no clinical evidence for reinfarction during the follow-up period, or (2) the patient underwent bypass surgery and either the native infarct artery or its graft was patent at follow-up. The other 6 patients either failed to reperfuse acutely or reperfused but suffered subsequent rethrombosis.

Exercise responses: With exercise, there was a significant increase in end-diastolic volume, stroke volume, heart rate and cardiac output. Increases in global ejection fraction and in regional wall motion, which are normalized for heart size, were more modest (Table II).

The global ejection fraction response to exercise correlated poorly with the exercise-induced change in wall motion in both the infarct site ($r = 0.38$, Figure 2) and the noninfarct region ($r = 0.47$). In 15 (63%) of the 24 patients, there was discord between the exercise response of the infarct and noninfarct regions, i.e., motion increased in 1 region but decreased in the other. In only 8 (53%) of these 15 did the ejection fraction response follow the infarct region's wall motion change. The ejection fraction response was determined mainly by the change in anterior wall motion ($r = 0.71$, $p < 0.001$, Figure 3) and was little influenced by the inferior wall ($r = 0.16$, Table III). Similar results were obtained in the patients recalled late (>6 months) after infarction ($n = 9$) as in patients entered into the study early (<6 weeks) after infarction ($n = 12$).

The left anterior descending artery perfuses twice as much myocardium as the right coronary artery[11] and, therefore, anterior wall motion would be expected to influence the ejection fraction more. To investigate the poor correlation between anterior wall motion and ejection fraction in patients with anterior infarction, we assessed the relation between motion in the infarct and noninfarct regions. There was an inverse correlation between the motion of the infarct and the noninfarct regions ($r = -0.57$, $n = 13$, $p < 0.05$), indicating discordance between the exercise responses of the 2 walls of the ventricle. This was not due simply to an exercise-induced change in the translational motion of the heart within the chest, because changes in the angle between the end-diastolic and end-systolic long axes were small and insignificant with exercise, and did not correlate with changes in regional wall motion. When partial correlation analysis was used to determine the relation between each wall and the ejection fraction while adjusting for the influence of the other wall, the ejection fraction correlated more highly with the function of the anterior wall than with the inferior wall, as indicated by the partial correlation coefficients (Table III). In patients with inferior wall infarc-

TABLE III Correlation Between Global and Regional Function Response to Exercise

Regional Wall Motion Response to Exercise	Correlation with EF Response (r)	(Partial r*)	(n)	p Value
Infarct region, all patients	0.38		24	NS
Anterior infarct	0.39	0.53	13	NS
Inferior infarct	0.82	0.83	11	0.001
Noninfarct region, all patients	0.47		24	NS
Anterior infarct	0.08	0.40	13	NS
Inferior infarct	0.32	0.38	11	NS
Anterior wall, all patients	0.71		24	0.001
Inferior wall, all patients	0.16		24	NS

* Partial correlation with respect to motion in the opposite wall; EF = global ejection fraction; NS = not significant.

TABLE IV Comparison of Ejection Fraction and Wall Motion Response with Exercise in Reperfused and Nonreperfused Patients

	Reperfused (n = 18)	Nonreperfused (n = 6)	Univariate F	p Value	Multivariate F	p Value
Ejection fraction (%)						
Rest	52 ± 12	57 ± 8	1.17	0.291		
Exercise	55 ± 12	57 ± 9	0.19	0.668	1.70	0.206
Rest-exercise	3 ± 5*	0 ± 8	1.53	0.229		
Regional wall motion in infarct site, SD/chord						
Rest	−2.3 ± 0.9	−2.7 ± 0.5	1.07	0.312		
Exercise	−2.1 ± 1.0	−2.9 ± 0.6	3.87	0.062	5.46	0.029
Rest-exercise	0.2 ± 0.5	−0.2 ± 0.2†	4.33	0.049		

* Paired *t* test, p <0.01; † paired *t* test, p <0.05; SD = standard deviations from the mean of normal reference group.

tion, the motion of the anterior and inferior walls was unrelated.

Correlation between exercise response and perfusion status: In reperfused patients, exercise led to an increase in ejection fraction but not in wall motion in the infarct region. Nonreperfused patients had a significant worsening of motion in the infarct region but no change in global function. Both groups had small increases in the motion of the noninfarct region with exercise. Discriminant analysis revealed that reperfused and nonreperfused patients were better distinguished by measurements of wall motion during exercise than by the ejection fraction response to exercise (Table IV).

In reperfused patients who had improvement of wall motion in the infarct site after exercise, the residual stenosis in the infarct artery was slightly milder than that in reperfused patients without a positive exercise response, both immediately after thrombolysis (77 ± 24 [n = 12] vs 83 ± 13% [n = 6], difference not significant) and at follow-up (58 ± 35 vs 60 ± 38%, difference not significant). Thus, the failure to increase function with exercise probably reflected a lack of salvage rather than continuing ischemia. In the noninfarct region, motion was more likely to increase after exercise in patients with 1-vessel than those with multivessel disease (71% of 14 vs 30% of 10, difference not significant).

Discussion

This study examined the effect of exercise on left ventricular function in patients receiving thrombolytic therapy for acute myocardial infarction. The data indicate that the regional exercise response in the infarct site reflects the reperfusion status of the infarct artery more accurately than the global ejection fraction response.

These results agree with data from previous studies demonstrating the relative insensitivity of the *resting* global ejection fraction in reflecting the function of the infarct region.[5,12,13] As seen in these rest studies, the exercise response in the noninfarct region may significantly affect global function. As a result, the ejection fraction response to exercise may underestimate the severity of an ischemic response in the infarct site, i.e., worsening of regional hypokinesis, if the noninfarct region responds normally, with an increase in motion. The ejection fraction may also overestimate the functional response of the infarct region if motion in the noninfarct region responds concordantly. It is, there-

fore, not surprising that the regional response to exercise more accurately reflects the reperfusion status of the infarct artery than does the global ejection fraction response.

In the present study, discordance between regional and global function was observed at a low level of exercise. Similar discordance has been reported by others at all levels of exercise using noninvasive imaging techniques. Schneider et al[14] reported that discordance between the ejection fraction and the wall motion score, a visual estimate of the extent of regional hypokinesis, occurred as often at 25 to 50 watts as at higher levels of exercise. Others have also found discordance between regional and global left ventricular functional responses to maximal, symptom-limited exercise.[15-18] Applegate et al[19] found the regional response to be more predictive of morbid events after infarction than did the change in ejection fraction. The present study complements these by measuring the magnitude of hyperkinesis in the noninfarct region and its response to exercise, and by quantitatively demonstrating its influence on the exercise ejection fraction.

A limitation of our study is the long follow-up time from infarction to exercise study in some patients. However, all of the patients were clinically stable in the interim and results were similar in the subgroups studied <6 weeks and >6 months after infarction. Others have reported that the ejection fraction exercise response is stable 3 to 8 weeks after infarction[20] 1 to 4 months after infarction[2] and between 2 weeks and 6 to 14 months after infarction.[4]

To avoid motion artifact, ventriculography was performed immediately after rather than during exercise. Although this may affect measurement of the functional response to exercise, reports on the duration of transient wall motion abnormalities vary from <3 to >30 minutes after cessation of exercise,[21,22] with dependence on the extent of coronary artery diease[23] and on the severity of left ventricular dysfunction.[24] Furthermore, the left ventricular functional response measured at peak exercise is predicted by changes seen immediately afterwards using 2-dimensional echocardiography in postinfarct patients.[19] Because all of our patients had a myocardial infarction and many had multivessel disease, the duration of the abnormalities would probably have been long enough to be captured in the ventriculograms.

We measured left ventricular function from single-plane ventriculograms because these provide more accurate volume determination than biplane studies.[25] For comparison, wall motion was also calculated in this view, which is more sensitive in detecting hypokinesis due to coronary artery stenosis or myocardial infarction.[26,27]

Clinical implications: It is not the intent of this study to advocate exercise contrast ventriculography. Instead, our data indicate that the global ejection fraction response to exercise is significantly influenced by motion in both the infarct and noninfarct regions, and that the response to exercise in the noninfarct region may oppose and dominate that of the infarct region. This imprecision of the global ejection fraction may explain its insensitivity compared with the regional response in predicting recurrent ischemic events after myocardial infarction.[3] However, an evaluation of the prognostic value of measuring the regional as compared with the global exercise response is beyond the scope of the present analysis and will require further study. We conclude that measurement of the ejection fraction response to exercise in patients studied after myocardial infarction estimates the net function of all regions of the left ventricle. However, to evaluate salvage of myocardium following thrombolytic therapy from the rest-exercise response, regional wall motion in the infarct site should be measured.

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Use of Initial ST-Segment Deviation for Prediction of Final Electrocardiographic Size of Acute Myocardial Infarcts

HARRY R. ALDRICH, MD, NANCY B. WAGNER, BA, JANE BOSWICK, BS, ANNE T. CORSA, MD, MICHAEL G. JONES, BA, PEER GRANDE, MD, KERRY L. LEE, PhD, and GALEN S. WAGNER, MD

The decision to administer thrombolytic therapy for limitation of acute myocardial infarction (AMI) size must occur when only the history, physical examination and 12-lead electrocardiogram of a patient are available. A method that could quickly assess the amount of jeopardized myocardium would greatly aid the physician. This study developed formulas from 68 anterior and 80 inferior AMI patients using the extent of initial ST-segment deviation (STΔ) to predict the final AMI size estimated by the Selvester QRS score in a population not receiving reperfusion therapy. Inclusion required: initial anterior or inferior AMI; admission electrocardiograpm $\leq$8 hours after the onset of symptoms with evidence of epicardial injury; elevated creatine kinase-MB; a predischarge electrocardiogram taken $\geq$72 hours after admission; and no AMI extension before the predischarge electrocardiogram. The extent of epicardial injury was quantified by counting the number of leads with $\geq$0.1 mm STΔ, by the sum (Σ) of STΔ in all leads and by the ΣSTΔ in the lead groups associated with each AMI location. These results were compared to the AMI size estimated from the predischarge electrocardiogram. Univariable and multivariable analyses generated these formulas for AMI size:

anterior = 3[1.5(number leads ST$\uparrow$) − 0.4];
inferior = 3[0.6(ΣST$\uparrow$ II, III, aVF) + 2.0].

Thus, formulas based on quantitative measurements of STΔ on the admission electrocardiogram are predictive of final QRS-estimated AMI size, and may be useful in determining the efficacy of acute reperfusion therapy.

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Information on the standard 12-lead electrocardiogram during the course of acute coronary occlusion has been useful in a variety of clinical settings. The admission electrocardiogram has been valuable in acute myocardial infarction (AMI) diagnosis and as a predictor of in-hospital complications.[1,2] The extent of epicardial injury (STΔ), reflected by either ST elevation (ST$\uparrow$) or depression (ST$\downarrow$), has been shown to estimate the amount of myocardium in jeopardy and the subsequent prognosis.[3–8] With the current use of emergent reperfusion therapies to limit AMI size, careful examination of the presenting electrocardiogram becomes increasingly important. Quantitative methods that could quickly estimate the amount of myocardium in jeopardy, and thereby identify the patients most likely to benefit from reperfusion therapy, would be of great clinical value.

Comparison between the estimated sizes of initially jeopardized myocardium and the resultant AMI size in the absence of reperfusion therapies could form a basis for determining the effectiveness of such interventions. Since many techniques for quantifying AMI size are expensive and difficult to perform, the inexpensive, clinically versatile electrocardiogram provides an attractive alternative.[9,10] One such method, the Selvester QRS scoring system,[11] awards points for abnormal characteristics of the QRS complex to provide a quantitative estimate of the size of single AMIs. The efficacy of this system has been evaluated extensively in postmortem correlations,[12–14] normal subjects[15,16] and many clinical studies.[17–19]

From the Department of Medicine, Duke University Medical Center, Durham, North Carolina, and the Department of Cardiology, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark. This work was supported in part by research grants HL-17670 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received August 10, 1987; revised manuscript received and accepted November 23, 1987.

Address for reprints: Galen S. Wagner, MD, Box 31211, Duke University Medical Center, Durham, North Carolina 27710.

TABLE I ST-Segment Criteria from the Admission Electrocardiogram*

Inclusion (All)	AMI Location
ST↑ ≥1 mm in ≥1 lead Max ST↑ ≥ max ST↓ or Max ST↓ in V_1 through V_3 ST↑ in V_2>V_1	Anterior max = ST↑ V_1 through V_3 Inferior max = ST↑ in II, III, AVF or ST↓ in V_1 through V_3

*Measured at J point all leads but aVR.
AMI = acute myocardial infarction; ↓ = depression; ↑ = elevation; max = maximum.

TABLE II Correlation of ST Deviation with AMI Size

AMI Location	ST Parameters	r
Anterior	Number of leads with ST↑	0.72
	ΣST↑ all leads	0.52
	ΣST↑ V_1 through V_3	0.38
	ΣST↑ V_1 through V_6	0.48
	ΣST↑ V_1 through V_3, I, aVL	0.46
Inferior	Number of leads with STΔ	0.50
	ΣST↑ all leads	0.61
	ΣST↑ all leads + ΣST↓ V_1 through V_3	0.60
	ΣST↑ II, III, aVF	0.61
	ΣST↑ II, III, aVF + ΣST↓ V_1 through V_3	0.59

Δ = change; Σ = sum; other abbreviations as in Table I.

The purposes of this study were to use the admission and discharge electrocardiograms to (1) determine the relations between the extent of initial STΔ and final AMI size by QRS score in anterior and inferior locations, and (2) develop formulas for each location to predict the final electrocardiographic estimation of AMI size from the initial STΔ.

Methods

Patient population: Between January 1965 and December 1981, consecutive patients admitted to Duke University Medical Center with a first AMI who did not receive thrombolytic therapy were screened.[20] Patients with the following characteristics were included: no clinical or electrocardiographic evidence of a previous AMI; admission heart rate ≤110 beats/min[21]; total creatine kinase ≥130 U/liter with presence of creatine kinase-MB; an "admission electrocardiogram" ≤8 hours after the acute onset of symptoms with evidence of epicardial injury (Table I); a "predischarge electrocardiogram" ≥72 hours after admission showing no AMI extension; and no complete left or right bundle branch block, anterior or posterior fascicular block, left or right ventricular hypertrophy or ventricular pacing on either electrocardiogram.[22]

Quantitative electrocardiographic analysis: The admission electrocardiogram was used to determine the extent of epicardial injury (STΔ) and to divide the patients into anterior or inferior AMI location based on the lead with the maximal deviation (Table I). Those who had concurrent elevation in leads I, aVL, V_5 or V_6 were classified as anterior or inferior according to the location of their primary change. Using the TP segment as the isoelectric line, ST↑ was measured manually to the nearest 0.5 mm (0.1 mV = 1 mm) in each lead except aVR at these intervals: J point, J + 40 ms and J + 80 ms. ST↓ was measured in the same way in leads V_1 through V_3, where it could have been caused by epicardial injury. The number of leads with ≥1 mm STΔ present, the sum (Σ) of the STΔ in all leads and the ΣSTΔ in the lead groups according to AMI location were determined (Table II).

Final AMI size was estimated from the Selvester QRS score on the predischarge electrocardiogram. This scoring system and its method of application have been described in detail elsewhere.[16,23] It was designed to contain a maximum of 32 points from consideration of 54 criteria, with each point representing approximately 3% infarction of the left ventricle.[11]

Data analysis: Quantification of epicardial injury was performed at each of the 3 intervals along the ST segment and compared with final AMI size. Although the correlations were similar for each of the intervals, the J point relation was slightly better. Thus, all subsequent analyses consider only measurements performed at the J point. All patients were analyzed according to the number of leads with ST↑, and by the 4 lead combinations associated with each of the MI locations (Table II). Pearson correlation coefficients, denoted by "r," were used to evaluate the relations among the ST parameters and the final AMI size.

Multivariable analyses using linear regression models were used to generate formulas from these ST determinations to predict the final AMI size for each location. The square of the multiple correlation coefficient, R^2, was used to describe the percent of variability of the AMI size accounted for by the ST-segment parameters in the regression models. Multivariable regression was also used to assess the degree to which duration of chest pain before the admission electrocardiogram might influence the formulas for predicting AMI size. The median absolute differences between the actual AMI size and that predicted from the formulas were determined for both locations according to the duration of chest pain.

Results

Of the 148 patients included in the study, 68 had an anterior AMI (48 men, 20 women; mean age 57, range 35 to 85) and 80 had an inferior AMI (62 men, 18 women; mean age 58, range 35 to 83) as defined by the criteria in Table I.

While the distributions of the number of leads with STΔ were similar for both AMI locations (Figure 1A), the ΣSTΔ varied significantly. As seen in Figure 1B, the ΣST in the anterior AMI patients ranged from 1 to 44 mm, with a median value of 9 mm. In contrast, in the inferior AMI patients the ΣST ranged from 1 to 28 mm, with a median value of 6.5 mm ($p = 0.04$). While the distributions of AMI size (Figure 2) were similar, the anterior group tended to have larger AMIs than the inferior group (respective median values 21% vs 15%, $p = 0.03$).

The relation of the ST parameters with AMI size are shown in Table II. For anterior AMI, the number of leads with ST↑ provided a stronger correlation than did ΣST↑ in any of the lead combinations. Conversely, the ΣST in the various lead combinations achieved stronger correlations than did the number of leads in the inferior AMI group. Although the ΣST↑ in all leads and the ΣST↑ in II, III and aVF both attained correlation coefficients of 0.61, the latter was considered to be preferable as it required quantification from only 3 versus 11 leads.

The formula for prediction of anterior AMI size that resulted from multivariable regression analyses was determined to be:

Anterior AMI = 3 [1.5 (number leads ST↑) − 0.4].

After consideration of the number of leads with ST↑, no other parameter added significantly to the predictive ability of this model. The Pearson correlation coefficient was r = 0.72. The square of this quantity (R^2) accounted for 52% of variability of the AMI size by the ST deviation factors in the regression models. The mean square error was 8.05.

For inferior AMI size prediction, multivariable regression analyses determined that:

Inferior AMI = 3 [0.6 (ST↓ II, III, aVF) + 2.0].

The Pearson correlation coefficient was r = 0.61. The R^2 accounted for 37% of variability of the AMI size by the ST-deviation factors in the regression models. The mean square error was 8.63. In these patients, consideration of the ΣST↓ in leads V_1 through V_3 further increased the variability in the final AMI size, which could be accounted for by ΣSTΔ from 37% to 39% but this was not a significant improvement. No other variables contributed additional significant information.

The duration of chest pain was assessed to determine its influence on the formulas. In Table III, the median absolute difference between the predicted AMI from the model and the observed AMI are stratified according to the duration of chest pain. The similarities in the median absolute difference for each time period illustrate that the formula is not influenced by the duration of chest pain within the first 8 hours of symptoms.

Discussion

Attempts to correlate initial epicardial injury with various electrocardiographic and enzymatic measures of AMI size have achieved differing results,[7-10,24] perhaps due in part to the limitations of both methods. The present study also has several inherent methodologic limitations. While STΔ at the J point was used for all analyses it had only a slightly (although not significantly) stronger correlation with AMI size than measurements performed at either J + 40 ms or J + 80 ms. Further, the amount of myocardial necrosis that had transpired before or after the admission electrocardiogram could not be considered since the Selvester score has not been validated for use in the presence of epicardial injury. Such quantification would likely be important in patients with "rapidly developing" AMI who have a quickly occurring increase and decrease in their ST segments, with concurrent QRS evolution.[25,26]

Although the duration of chest pain did not appear to affect the accuracy of the formulas (Table III), it is difficult to determine the exact time of onset of symptoms in patients with either intermittent pain or "silent" ischemic episodes. Other factors that may have

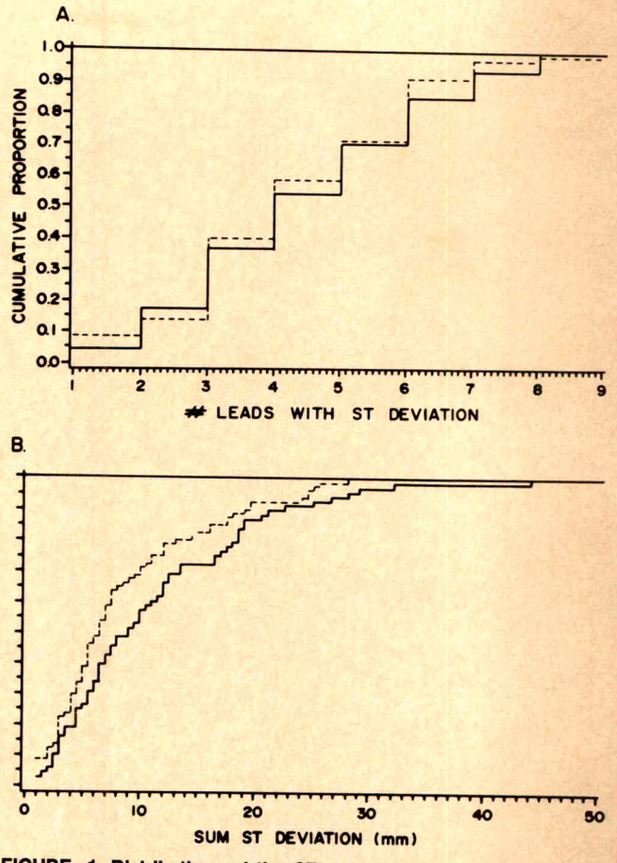

FIGURE 1. Distributions of the ST-segment parameters. Anterior and inferior acute myocardial infarct locations are combined. In *A*, the cumulative proportion of patients with from 1 to 9 leads of ST-segment deviation is shown. (See text.) In *B*, the sum of ST-segment deviation in millimeters is shown.

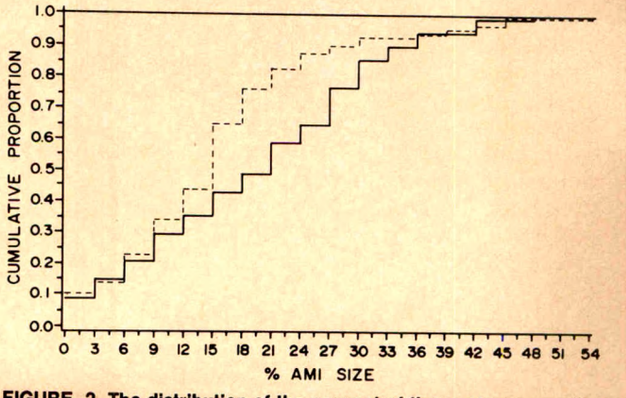

FIGURE 2. The distribution of the percent of the acute myocardial infarct (AMI) size from the predischarge standard 12-lead electrocardiogram is shown for all patients.

TABLE III Duration of Chest Pain Versus Absolute Median Difference Between Predicted and Measured AMI Size

AMI Location	Pain Duration (hrs)	Pts (n)	Difference in AMI Size
Anterior	0–2	22	5.7
	2–4	22	4.5
	4–6	9	6.9
	6–8	15	5.7
Inferior	0–2	37	4.8
	2–4	24	6.6
	4–6	8	6.0
	6–8	11	5.1

AMI = acute myocardial infarction.

influenced the results in this study include the limitations intrinsic to the electrocardiogram such as lack of equipment standardization, degree of patient recumbency, respiratory variation, chest wall dimensions and lung volume. Finally, it is essential that the formulas proposed in this study be validated in a comparable test population before general application.

In the anterior AMI group, the number of leads with ST↑ was a more important variable (r = 0.72) than ΣST (r = 0.52) for predicting AMI size. Using precordial mapping studies, Murray et al[27] also found a significant correlation between the number of sites with ST↑ and a radionuclide estimate of myocardial necrosis. Cohen et al[28] determined that the percent of anterior wall asynergy during left anterior descending coronary artery angioplasty correlated with both the number leads with ST↑ and ΣST↑ on a simultaneous 12-lead electrocardiogram. Hackworthy et al[7] have demonstrated an excellent correlation between ΣST↑ and final QRS score by the simplified Selvester system.[15]

The ΣST in leads II, III and aVF is a more important variable for predicting inferior AMI size (r = 0.61) than the number of leads with STΔ (r = 0.50). The study by Cohen et al[28] also showed good correlations between the percent of inferior wall asynergy and both the number of leads with ST↑ and ΣST↓.

The ΣST↓ V_1 through V_3 provided some additional information. Precordial ST↓ with inferior AMI has been associated with a larger size, more frequent complications and a poorer prognosis.[5,6,29,30] However, others have indicated that ST↓ is simply a reciprocal electrical phenomenon.[31] In patients with inferior AMI, Hlatky et al[6] reported a relation between ST↓ V_1 through V_3 and QRS evidence of posterior involvement. However, they found that the ratio of initial ST↓ to final QRS points in V_1 through V_3 was much lower than the ratio of initial ST↑ to final QRS points in II, III and aVF. In the present study, inclusion of ΣST↓ V_1 through V_3 in the model increased the R^2 value only slightly when optimally weighted at a 1:4 ratio with the ΣST↑ II, III, aVF (from 37% to 39%). Thus, these results support the concept that the ΣST↓ V_1 through V_3 is primarily the reciprocal of ΣST↑ in II, III and aVF, but it may also be minimally indicative of additional ischemia.

Recent studies have investigated the relation between the extent of STΔ and subsequent AMI size. In a study by Bar et al,[8] patients were randomized to either intravenous streptokinase or control therapy. Limitation of AMI size occurred primarily in patients with the greatest admission ΣST↑. Hackworthy et al[32] found that rapid resolution of ΣST during the first 8 hours was associated with spontaneous opening of the left anterior descending artery and smaller anterior AMI. No such relations were found in patients with inferior AMI.

With the many emergent therapeutic alternatives for AMI size limitation, methods that can quickly identify the patients most likely to benefit are necessary. The formulas proposed in the present study indicate the "natural" extent of the evolving AMI, and thus may be valuable both in patient selection for acute intervention and in the subsequent evaluation of the efficacy of such therapy.

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Usefulness of Lactate Dehydrogenase and Lactate Dehydrogenase Isoenzymes for Diagnosis of Acute Myocardial Infarction

GREGG J. REIS, MD, HARVEY W. KAUFMAN, MD, GARY L. HOROWITZ, MD, and RICHARD C. PASTERNAK, MD

The usefulness of lactate dehydrogenase (LD) and LD isoenzymes in the diagnosis of acute myocardial infarction (AMI) is controversial. The present study reviewed 507 consecutive patients in whom creatine kinase, creatine kinase isoenzymes, LD and LD isoenzymes were ordered over a 1-month period. Of these, 249 had an insufficient number of serial enzyme determinations to establish a laboratory diagnosis of AMI. After excluding an additional 11 patients for other reasons, 247 patients remained for analysis. Of these, only 2 (0.8%) had myocardial infarction by standard clinical criteria with normal creatine kinase and creatine kinase-MB but elevated LD and abnormal LD isoenzymes. Seven patients (7 of 247, 2.8%) had false-positive LD isoenzymes. Thus, the routine use of LD and LD isoenzymes was of no use in most patients (96%) and led to the incorrect diagnosis of AMI more than 3 times as often as it helped with a correct diagnosis. Total 1-month charges for all the LD and LD isoenzymes obtained equalled $42,450. Therefore, it appears that LD and LD isoenzymes are not routinely useful in the diagnosis of AMI and may result in considerable unnecessary expense. It is suggested that LD and LD isoenzymes be ordered only under suspicion of late presentation (>48 hours) of AMI.

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Over the last 30 years, serial serum enzyme determinations have become the "gold standard" by which acute myocardial infarction (AMI) is diagnosed. This period has seen a gradual change in both the enzymes measured and the methods used, as older assays have been supplemented by more sensitive and specific techniques. The first serum enzyme reported elevated in AMI, in 1954, was asparatate aminotransferase.[1] The introduction of lactate dehydrogenase (LD)[2] and its isoenzymes[3,4] over the next several years provided increased specificity. However, with the introduction of creatine kinase (CK),[5] and particularly the MB isoenzyme,[6] an even more sensitive and specific assay was introduced. Numerous studies have confirmed the value of the CK-MB assay for the diagnosis of AMI.[7–11]

The use of LD and its isoenzymes has been more controversial. Several recent articles[12–18] recommend that CK and CK-MB be the only enzyme studies performed for the routine diagnosis of AMI. However, other analyses of available data[8,11,19–24] have recommended routine measurement of LD and LD isoenzymes, or measurement in cases of burns or trauma.[25] The present study was designed to determine the incremental benefits and potential costs of LD and LD isoenzymes in the diagnosis of AMI. Whereas previous studies have focused on patients admitted to coronary care units, this study also included patients in whom a relatively low suspicion of AMI led to admission to an electrocardiographically monitored bed *outside* of the intensive care unit.

Methods

The patient population consisted of 507 consecutive patients in whom CK, CK-MB, LD and LD isoenzymes

From the Charles A. Dana Research Institute and Harvard-Thorndike Laboratory, and the Cardiovascular Division and Department of Pathology, Beth Israel Hospital, Boston, Massachusetts. Manuscript received October 1, 1987; revised manuscript received December 15, 1987, and accepted December 16.

Address for reprints: Richard C. Pasternak, MD, Beth Israel Hospital, 330 Brookline Avenue, Boston, Massachusetts 02215.

were measured at Beth Israel Hospital during a 1-month period. The patients were identified by review of the computerized records of the chemistry laboratory. If patients had consecutive enzyme measurements extending into the preceding or following month, these also were included. In order to have sufficient enzyme measurements for inclusion into the study, at least 3 values of CK and CK-MB over 48 hours and at least 1 value of LD and LD isoenzymes were obtained.

All our samples were handled according to our laboratory's standard procedures. They were centrifuged upon receipt and the serum was separated into 3 aliquots for proper storage until analysis, which always occurred within 24 hours. The original aliquot was used to measure total CK and LD, a frozen aliquot was used for CK isoenzymes and a room-temperature aliquot for LD isoenzymes. Total CK and LD activities were determined at 37° using Roche CK-NAC reagent and Roche LD reagent on a Roche COBAS-BIO centrifugal analyzer (Roche Diagnostic Systems). Activities of CK and LD isoenzymes were determined by agarose gel electrophoresis using Corning reagents (Corning Medical) and scanning densitometry using a CDS-200 densitometer (Beckman Instruments) in the fluorescent mode. Each agarose gel was visually examined to establish the presence of CK-MB before quantitation. As has been standard practice in our laboratory for many years, specimens in which total LD was within the normal range did not undergo LD isoenzyme analysis.

All serum enzyme values were reviewed by a clinical pathologist unaware of the patient history. This analysis alone served to initially classify them as positive for infarction, negative for infarction or equivocal.

Positive CK and CK-MB were defined as (1) total CK >200 IU/liter with CK-MB ≥5% on 1 specimen, or (2) total CK ≤200 IU/liter, but with CK-MB ≥5% on peak specimen, and rise and fall on serial specimens. Equivocal CK and CK-MB consisted of CK-MB ≥5%, with total CK ≤200 IU/liter and without typical rise and fall. Positive LD isoenzymes were defined as LD1 ≥LD2 on any specimen; otherwise, patients were classified as having negative LD isoenzymes.

We reviewed the charts of all patients in whom total CK, CK-MB or LD isoenzymes were abnormal (CK >200 IU/liter, CK-MB ≥5% of total CK or LD1 ≥LD2), or in whom CK rose ≥50% from baseline values. Patients with entirely normal, CK, CK-MB *and* LD isoenzymes were characterized as negative for infarction without further review. In patients whose charts were reviewed, clinician's discharge diagnosis, discharge status, clinical history and electrocardiograms were noted. Five patients transferred from other institutions with documented AMI but whose enzyme values had not yet returned to normal were excluded, as were 2 patients whose charts could not be located. Four patients with cardiac enzyme elevation after cardiac surgery also were excluded.

Unequivocal electrocardiographic changes were defined as persistent new Q waves; equivocal changes as persistent ST- or T-wave abnormalities, transient Q waves or a conduction disturbance.

The diagnosis of AMI was based on the standards of the World Health Organization as revised in 1979.[26] Definite AMI was defined as (1) positive CK and CK-MB, or (2) unequivocal electrocardiographic changes. Patients with positive LD isoenzyme values were considered to have definite AMI if they had equivocal or unequivocal electrocardiographic changes or positive CK-MB *and* elevated LD in a typical pattern for AMI. Possible AMI was defined as equivocal electrocardiographic or enzymatic abnormalities. In the absence of these changes, patients were classified as negative for AMI.

Laboratory tests were ordered as part of the routine care of these patients, with both house officers and attending physicians able to initiate these orders. Total laboratory charges were calculated from the per-test charges in effect at the time of the study. Charges were $6 per total LD assay and $42 per LD isoenzyme analysis.

Test performance parameters were defined as follows: true positive: patients with a positive test result and definite AMI; false positive: patients with a positive test result but without definite AMI; true negative: patients with a negative test result and without definite AMI; false negative: patients with a negative test result but with definite AMI; sensitivity: (all true positives)/(all patients with definite AMI); specificity: (all true negative)/(all patients without definite AMI).

Results

Of the 507 consecutive patients in whom some measurement of CK and LD were made during the 1-month period of this study, 249 (49%) had insufficient serial enzymes (fewer than 3 values of CK and CK-MB, or no measurement of LD isoenzymes) to be included. Many of these patients had enzyme studies performed for noncardiac conditions. However, as has been noted in previous studies,[21] it is likely that many tests were ordered in a manner that precluded their use in diagnosing AMI, even though the tests were ordered for that purpose. In order to ascertain whether any of the excluded patients may have had positive enzyme studies on the first 2 specimens, and thus had not had a third sample drawn, the charts of all excluded patients with CK-MB >10 IU/liter, or with LD1 ≥LD2 on any specimen, were reviewed. Of the 249 excluded patients, 14 met 1 or both of these criteria; of these, 9 were undergoing cardiac surgery, 1 had rhabdomyolysis and 4 had a single value of LD1 ≥LD2. These 4 patients had another value of LD isoenzymes within 16 hours of the abnormal value with LD1 <LD2, had no diagnostic electrocardiographic changes and were not considered to have had an AMI by their physicians.

As noted, 11 patients with adequate enzyme studies were excluded after chart review revealed conditions (cardiac surgery, post-AMI transfer, chart unavailable) that could potentially confound analysis of their serum enzymes. Of the remaining 247 patients, 29

TABLE I Summary of Laboratory and Clinical Findings

	Definite AMI			Possible AMI
	+CK/+MB (n = 20)	−CK/+MB (n = 7)	+LD only (n = 2)	(n = 6)
Age (yrs)	73 ± 2	78 ± 1	59 ± 1	76 ± 3
CK peak (IU/liter)	906 ± 219	126 ± 8	546 ± 344	195 ± 42
MB peak (IU/liter)	95 ± 41	12 ± 0	15 ± 11	13 ± 4
LD peak (IU/liter)	735 ± 240	278 ± 40	533 ± 219	246 ± 59
LD1 ≥ LD2	11 (55%)	1 (14%)	2 (100%)	0
ECG changes				
Q-wave	7 (35%)	1 (14%)	1 (50%)	0
Non-Q-wave	12 (60%)*	6 (86%)*	1 (50%)	3 (50%)
Chest pain	15 (75%)	6 (86%)	2 (100%)	4 (67%)
Death	6 (30%)	2 (28%)	0	0

Figures for age and enzyme values represent mean ± standard error of the mean within each group.

* Includes 1 patient in each group with left bundle branch block.

AMI = acute myocardial infarction; CK = creatine kinase (normal ≤200 IU/liter); +CK/+MB = CK > 200 IU/liter, MB ≥ 5%; −CK/+MB = CK ≤200 IU/liter, MB ≥5% with typical serial rise and fall; ECG = electrocardiogram; LD = lactate dehydrogenase (normal ≤200 IU/liter); LD1,LD2 = LD isoenzymes 1 and 2; +LD only = LD1 ≥ LD2 with normal CK and MB; MB = creatinine kinase MB isoenzyme (normal <5% of total CK).

(12%) had definite AMI and 6 (3%) possible AMI. The results of enzyme studies, electrocardiographic analysis and clinical outcome are listed in Table I. It should be noted that the mean total CK in the patients listed as LD+ only is markedly elevated at 546 IU/liter. This was due to 1 patient who had a peak CK of 1,033 IU/liter with only 3% MB fraction on the initial specimen. As this was considered to be nondiagnostic, the positive LD isoenzyme analysis was taken as the only diagnostic enzyme marker of AMI.

Positive LD isoenzymes were noted in a total of 21 (9%) patients. Of these, 12 had unequivocally positive CK-MB values. There were 7 (2.8%) patients with positive LD isoenzymes in the absence of positive CK-MB, electrocardiographic or clinical criteria for infarction (false-positive LD isoenzymes). Of these 7 patients, 4 had a single elevated LD value with LD1 ≥LD2, but in each of these 4 cases there were other normal LD measurements within 24 hours of the single abnormal value. This was felt to be most consistent with a laboratory error or with hemolysis. One patient with widespread carcinoma of the lung had persistently elevated LD1 over several weeks. In the remaining 2 cases, there were several elevated LD values with LD1 ≥LD2 on at least 1 specimen without satisfactory explanation.

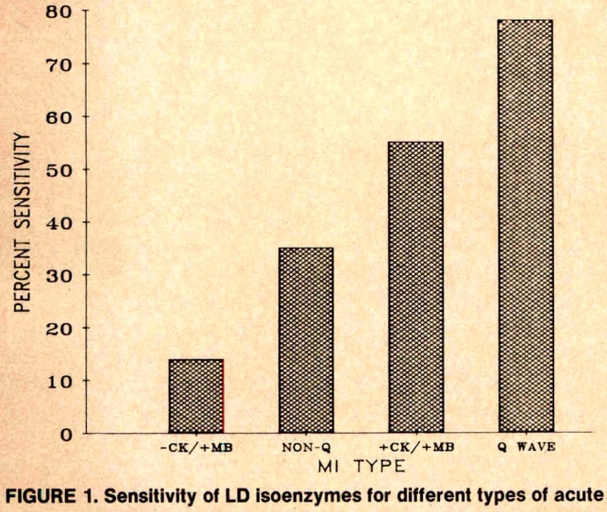

FIGURE 1. Sensitivity of LD isoenzymes for different types of acute myocardial infarction (MI). −CK/+MB = CK ≤200 IU/liter, CK-MB ≥5%, with pattern of serial rise and fall; +CK/+MB = CK >200 IU/liter, CK-MB ≥5%.

In only 2 cases (2 of 247, 0.8%), therefore, did LD isoenzymes provide the *only* confirmatory enzymatic evidence for a true AMI. Both patients had a clear onset of chest pain >48 hours (3 and 7 days, respectively) prior to initial enzyme measurements.

In our population, the sensitivity and specificity of LD isoenzymes for definite infarction were 48% and 97%, respectively. If possible infarctions were to be considered with true infarctions, sensitivity would fall to 40%. Sensitivity was lowest for infarctions with normal total CK but elevated CK-MB (14%) (when a high sensitivity would be most desirable), and highest for Q-wave infarctions (78%) (Figure 1).

A total of 2,035 LD assays and 720 LD isoenzyme assays were performed. Total charges for the 1-month period were $42,450, or an average of $83 per patient. If the 2 patients in whom the LD was the only positive enzyme are considered the only clinically useful result, the charge per useful result was $21,225!

Discussion

In the present study, measurement of LD and LD isoenzymes was not useful in the routine diagnosis of AMI in the vast majority of patients and resulted in a 2.8% incidence of false-positive results. In fact, among 247 patients, there were only 2 clinically helpful results in which true-positive LD isoenzyme studies helped to make the diagnosis of AMI in the patients presenting late (>48 hours) after the onset of symptoms. Despite a specificity of 97%, there were still 7 cases in which false-positive LD isoenzymes could have resulted in an incorrect diagnosis of AMI.

These findings support those of Heller et al,[27] who found that only 1% of patients with negative CK-MB had positive LD isoenzymes. Galen and Gambino,[8] in a study of 100 patients, found no cases in which LD isoenzymes were the only diagnostic marker of AMI. The rare cases in which LD isoenzymes may be useful can be predicted by awareness of the typical decay curves of CK, CK-MB and LD,[17,28] which suggest that patients presenting >48 hours after the onset of chest pain will have the highest probability of positive LD isoenzymes with normal CK and CK-MB. Patients with normal CK-MB and elevated but falling total CK values are most likely to be those presenting 48 to 96 hours after AMI.

The sensitivity and specificity of LD isoenzymes have been examined in many previous studies[11] and have averaged approximately 80 and 94%, respective-

ly. In contrast, the sensitivity of LD isoenzyme analysis for AMI in the present study (48%) was considerably lower and varied with the type of infarction. Out of 29 definite infarctions in our study, 9 (31%) were Q-wave (transmural), 18 (62%) were non-Q-wave (nontransmural) and there were 2 patients with preexisting left bundle branch block. There were 7 patients with "microinfarctions," defined as normal total CK but elevated CK-MB in a typical pattern for infarction.[29] LD isoenzyme sensitivity for "microinfarctions" has been reported to be only 10 to 28%[28-30] and only 1 of 7 patients (14%) in our group had abnormal LD isoenzymes. This was unfortunate, for additional confirmatory evidence of AMI would have been most helpful in this population. Sensitivity was higher for larger infarctions—55% in "macroinfarctions" (elevated total CK) and 78% in Q-wave infarcts. The relatively low sensitivity in the present study was related, at least in part, to the inclusion of patients outside of the coronary care unit. These were patients with a lower prior probability of infarction and generally smaller infarctions. Previous studies have generally included only patients admitted to a coronary intensive care unit. The low sensitivity of the LD isoenzyme assay makes it an especially poor test to "rule out" AMI and a negative result does not significantly alter the probability of an AMI having taken place.

In spite of the relatively high specificity of LD isoenzymes (97%), the number of false-positive results exceeded the number of *helpful* true positives, making the test potentially more misleading than useful. Fisher[12] noted an 8% incidence of positive LD isoenzymes in a group of patients without AMI. Galen et al[8] found 1 case of false-positive LD isoenzymes among 100 patients. The routine measurement of LD and LD isoenzymes in a population with a low prevalence of AMI further increases the risk of erroneous diagnosis of AMI, due to the relatively high number of false positives in relation to useful true positives, as was observed in the present study.

A potential source of bias in our study was the exclusion of a large number of patients. None of the patients excluded for inadequate enzyme studies clearly had an AMI; they were excluded because it was felt that AMI could not be ruled out. Indeed, 4 of these patients had positive LD isoenzymes without other clinical criteria for AMI and, had they been included, the number of false positives would have been higher. It is conceivable that some patients in the group with entirely negative serum enzyme studies (whose charts were not reviewed) had AMI indicated by electrocardiographic criteria only. If this was true, the number of false-negative tests would have been higher and the sensitivity correspondingly lower than previously stated.

It should be emphasized that laboratory charges, rather than actual costs, are cited to provide some insight into the fiscal impact of routine use of LD and LD isoenzymes. The actual costs of laboratory tests are difficult to assess, whereas charges provide a convenient benchmark for analysis and are grossly related to costs. Although savings from selective use of LD and LD isoenzymes would be considerable, they would certainly be less than indicated by the charge data.

Clinical implications: Patients with the highest probability of a useful positive LD isoenzyme result are those with a clinical history of chest pain beginning >48 hours prior to admission and with nondiagnostic CK-MB studies. In these cases, LD isoenzymes can be requested by the clinician even if such procedures are not performed routinely. Because LD isoenzymes are stable for several days at room temperature,[11] serum can be held aside for later analysis if it becomes necessary. Given the very high predictive value of CK-MB analysis, it is recommended that this assay be performed first in all cases. Only if CK-MB results are negative *and* there is a high suspicion of AMI presenting late, should LD isoenzyme analysis be requested.

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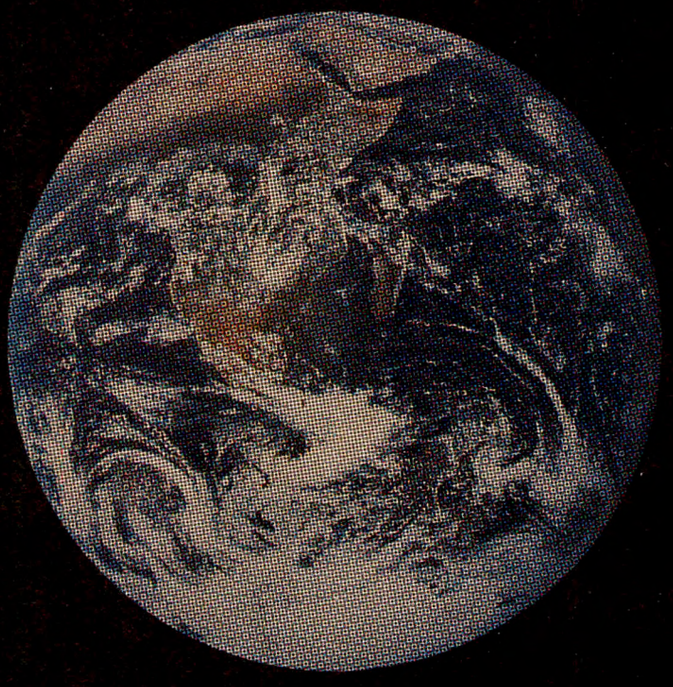

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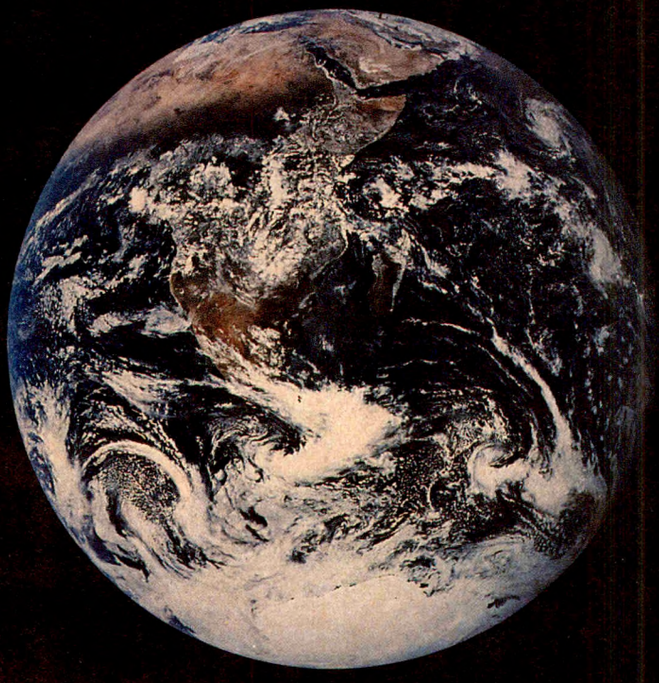

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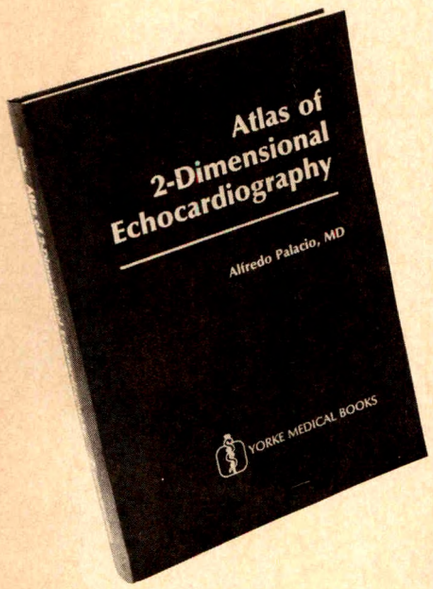

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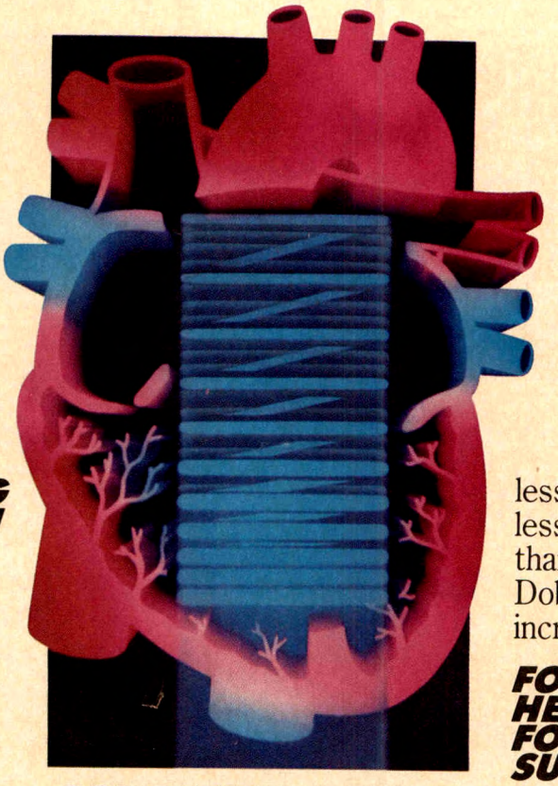

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Clinical Pharmacology: Dobutrex Solution is a direct-acting inotropic agent whose primary activity results from stimulation of the ß receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilative effects. It does not cause the release of endogenous norepinephrine, as does dopamine. In animal studies, dobutamine produces less increase in heart rate and less decrease in peripheral vascular resistance for a given inotropic effect than does isoproterenol.

In patients with depressed cardiac function, both dobutamine and isoproterenol increase the cardiac output to a similar degree. In the case of dobutamine, this increase is usually not accompanied by marked increases in heart rate (although tachycardia is occasionally observed), and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.

Facilitation of atrioventricular conduction has been observed in human electrophysiologic studies and in patients with atrial fibrillation.

Systemic vascular resistance is usually decreased with administration of dobutamine. Occasionally, minimum vasoconstriction has been observed.

Most clinical experience with dobutamine is short-term—up to several hours in duration. In the limited number of patients who were studied for 24, 48, and 72 hours, a persistent increase in cardiac output occurred in some, whereas the output of others returned toward baseline values.

The onset of action of Dobutrex Solution is within one to two minutes; however, as much as ten minutes may be required to obtain the peak effect of a particular infusion rate.

The plasma half-life of dobutamine in humans is two minutes. The principal routes of metabolism are methylation of the catechol and conjugation. In human urine, the major excretion products are the conjugates of dobutamine and 3-O-methyl dobutamine. The 3-O-methyl derivative of dobutamine is inactive.

Alteration of synaptic concentrations of catecholamines with either reserpine or tricyclic antidepressants does not alter the actions of dobutamine in animals, which indicates that the actions of dobutamine are not dependent on presynaptic mechanisms.

Indications and Usage: Dobutrex Solution is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to institution of therapy with Dobutrex.

Contraindications: Dobutrex Solution is contraindicated in patients with idiopathic hypertrophic subaortic stenosis and in patients who have shown previous manifestations of hypersensitivity to Dobutrex.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex Solution may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10% of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5% have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex Solution may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

3. *Hypersensitivity*—Reactions suggestive of hypersensitivity associated with administration of Dobutrex Solution, including skin rash, fever, eosinophilia, and bronchospasm, have been reported occasionally.

4. Dobutrex Solution contains sodium bisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Precautions: 1. During the administration of Dobutrex Solution, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex Solution.

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex Solution is instituted.

3. Animal studies indicate that dobutamine may be ineffective if the patient has recently received a ß-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex Solution following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex Solution for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clincial studies in which Dobutrex Solution was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10- to 20-mm increase in systolic blood pressure and an increase in heart rate of 5 to 15 beats/minute have been noted in most patients. (*See* Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5% of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3% of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex Solution have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex Solution until the patient's condition stabilizes. Because the duration of action of Dobutrex Solution is short, usually no additional remedial measures are necessary.

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Direct and Autonomically Mediated Effects of Oral Flecainide

PAOLO ALBONI, MD, NELLY PAPARELLA, MD, RICCARDO CAPPATO, MD, and GIAN CARLO CANDINI, PhD

This study was undertaken to determine if oral flecainide exerts autonomically mediated actions in addition to its direct depressant effect. Electrophysiologic studies were performed twice in each of 15 patients (mean age 59 years) with normal resting and intrinsic heart rate and normal A-H interval. In the first study, the variables of sinus node and atrioventricular node were evaluated both in the basal state and after autonomic blockade (propranolol 0.2 and atropine 0.04 mg/kg). Oral flecainide was administered for 4 to 5 days (200 to 250 mg daily) and the study was then repeated using the same methods. From comparison of data obtained in the 2 studies in the basal state, the overall effect of flecainide was evaluated and by comparing those obtained after autonomic blockade, the direct action of the drug was assessed. The overall effect of flecainide on sinus node was slight; sinus cycle length, corrected sinus node recovery time and sinoatrial conduction time did not change significantly after the drug. In contrast, after autonomic blockade the variables of sinosal automaticity were increased significantly ($p < 0.01$). Flecainide significantly prolonged the atrioventricular node variables both in the basal state and after autonomic blockade ($p < 0.01$), but the degree of increase was more marked after autonomic blockade ($p < 0.05$). These data show dual effects of oral flecainide: a direct depressant action and an autonomically mediated opposing action, likely of vagolytic type.

(Am J Cardiol 1988;61:759–763)

The electrophysiologic properties of flecainide have been examined in cardiac tissue preparations and the drug has shown direct depressant action on the cardiac fibers.[1-4] In the clinical setting flecainide prolonged atrial, atrioventricular (AV) nodal and infranodal conduction and to a slighter extent atrial, AV nodal and ventricular refractory periods.[5-9] The autonomic effects of the drug have not been investigated in great detail. It has only been shown by Cowan and Vaughan Williams,[1] both in vivo in the pithed rat and in vitro in isolated rabbit atria, that the drug has no significant antisympathetic effects. The same investigators have also demonstrated that flecainide has no "calcium-antagonist" action. The present study determines whether oral flecainide exerts autonomically mediated action in man, in addition to its direct depressant effect. We used a study protocol that investigates the different modes of action of an antiarrhythmic drug (Figure 1).

From the Division of Cardiology and Health Physics Department, Arcispedale S. Anna, Ferrara, Italy. Manuscript received September 22, 1987; revised manuscript received December 18, 1987, and accepted December 19.

Address for reprints: Paolo Alboni, MD, Division of Cardiology, Arcispedale S. Anna, 44100 Ferrara, Italy.

Methods

Patients: Electrophysiologic studies were performed in 15 patients (7 men and 8 women), 38 to 72 (mean 59 ± 10) years of age. The following criteria were used: (1) normal sinus rate (60 to 100 beats/min) in several resting standard electrocardiograms and no evidence of sinus node dysfunction in a 24-hour electrocardiographic recording and (2) normal observed intrinsic heart rate and normal A-H interval (<120 ms). The predicted intrinsic heart rate was estimated for each patient using the linear regression equation derived by Jose et al,[10] relating intrinsic heart rate to age.

All patients were studied for dizziness or syncope or involvement of intraventricular conduction. Ten patients had organic heart disease and 5 had no signs of underlying heart disease. Fourteen patients had syncope or dizziness, 3 right bundle branch block, 1 left bundle branch block and 2 bifascicular block. All

patients were in New York Heart Association class I. No patient had a recent myocardial infarction. Electrolytes and T_3 and T_4 values were within the normal range at the time of the study. All cardioactive medications and drugs having effects on the autonomic system were terminated before catheterization for a period that exceeded 5 half-lives of any agent.

Procedures: Informed signed consent was obtained from each patient and the studies were performed in the postabsorptive nonsedated state. A quadripolar catheter was introduced percutaneously via the femoral vein and positioned in the high lateral right atrium for stimulation and recording the atrial electrocardiogram. Another bipolar catheter was positioned across the tricuspid valve to record His bundle activity. Multiple surface electrocardiographic leads I, II, III and V_1 were recorded simultaneously with the intracardiac bipolar electrograms (frequency setting 0 to 20 Hz for surface electrocardiograms and 40 to 500 Hz for intracardiac electrocardiograms). All recordings were made at paper speeds of 50 to 100 mm/s. Atrial stimulation was performed using a programmable stimulator, the induced stimuli being 2 times the diastolic threshold and 2 ms in duration.

Ten minutes after the introduction of the catheters, the mean sinus cycle length was obtained by averaging 10 consecutive sinus cycles. Sinus node recovery time was measured by atrial pacing at 5 different rates, starting at a rate 20 beats/min above the spontaneous sinus rate to a rate of 170 to 180 beats/min. Pacing was performed for 60 seconds at each level. Ten sinus cycles were analyzed after termination of pacing and the longest interval was used to calculate the sinus node recovery time. The maximum corrected sinus node recovery time was calculated as previously described.[11,12] Sinoatrial conduction time was estimated by the continuous pacing method described by Narula et al[13]; the atria were paced at a rate of 6 to 7 beats/min higher than the sinus rate.

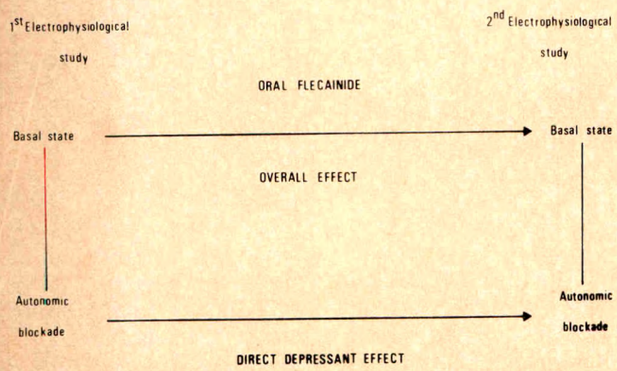

FIGURE 1. Study design. The electrophysiologic study was performed twice in each patient. In the first study the variables of sinus node and atrioventricular node, highly conditioned by autonomic system, were evaluated both in the basal state and after pharmacologic autonomic blockade. Oral flecainide was administered for 4 to 5 days and the electrophysiologic study was then repeated with the same methods. By comparing the data obtained in the 2 studies in the basal state, the overall effect of flecainide was evaluated. By comparing those obtained after autonomic blockade the direct action of the drug was assessed.

The following variables of AV nodal conduction were evaluated: A-H interval during sinus rhythm, A_1-H_1 interval at atrial cycle length of 600 ms, the longest atrial paced cycle for Wenckebach block and the AV nodal effective and functional refractory periods. To determine the latter, comparable atrial cycle lengths (A_1-A_1) were scanned with extrastimuli (A_2) after every eighth beat at progressively decreasing (by 10 ms) coupling intervals.

After this autonomic blockade was achieved.[10,12,14-16] Propranolol 0.2 mg/kg of body weight was administered intravenously over a period of 3 minutes. After 10 minutes, atropine sulfate 0.04 mg/kg was administered intravenously over 1 minute. After atropine administration, the shortest 10 consecutive sinus cycles were used to determine the mean intrinsic sinus cycle length. This reached a plateau at approximately 4 minutes and remained stable for approximately 30 minutes. At 5 minutes after atropine administration, measurements of sinus node and AV node variables were repeated, similar to those obtained in the basal state. These measurements were completed in less than 30 minutes. At the end of the study oral flecainide was administered at the dosage of 200 or 250 mg daily (patients weighing >70 kg) in 2 divided doses for 4 to 5 days. Electrophysiologic studies were then repeated with the same method, both during the basal state and after autonomic blockade, 2 hours after the last dose of flecainide. At the end of the electrophysiologic study, blood samples were drawn for the determination of plasma flecainide level[17] (therapeutic range 200 to 1000 μg/ml). Blood pressure was recorded by sphygmomanometer.

Statistical evaluations were performed using the Wilcoxon test (p value significant at ≤ 0.05). Results are given as mean ± standard deviation.

Results

Sinus nodal function: In the basal state flecainide did not significantly change sinus cycle length, corrected sinus node recovery time or sinoatrial conduction time (mean increases 3 ± 7%, 14 ± 37% and 8 ± 27%, respectively) (Figure 2, Table I). On the contrary, after autonomic blockade, flecainide significantly prolonged intrinsic sinus cycle length (13 ± 7%, $p < 0.01$), intrinsic corrected sinus node recovery time (56 ± 62%, $p < 0.01$) and intrinsic sinoatrial conduction time (33 ± 36%, $p < 0.01$). In all patients the intrinsic heart rate observed was within the normal range. The longest sinus node recovery time was always the first postpacing escape sinus beat in both studies. The degree of increase induced by the drug in sinus cycle length and corrected sinus node recovery time was significantly more marked after autonomic blockade than in the basal state ($p < 0.01$), whereas the degree of change in sinoatrial conduction time did not show significant differences.

TABLE I Effects of Flecainide on Sinus Nodal Functions in the Basal State and After Autonomic Blockade

Pt	SCL (ms)				CSRT (ms)				SACT (ms)			
	BS	F	AB	AB + F	BS	F	AB	AB + F	BS	F	AB	AB + F
1	596	598	579	713	403	270	180	273	210	138	112	197
2	806	917	692	787	450	423	247	350	198	227	104	113
3	889	859	723	757	340	374	327	762	211	238	107	137
4	680	702	673	743	227	254	250	407	146	154	119	123
5	941	932	823	1008	320	395	300	317	163	137	90	130
6	915	931	747	781	420	514	283	293	201	123	104	105
7	750	861	777	924	253	360	213	500	163	227	114	220
8	806	835	678	752	457	397	270	304	189	188	70	135
9	801	855	701	822	233	493	146	463	152	172	105	114
10	945	952	765	838	364	253	360	517	167	227	141	164
11	868	865	863	1080	410	360	485	523	131	188	155	143
12	890	900	827	883	363	336	323	300	185	205	175	170
13	726	745	658	678	183	303	180	300	156	118	117	120
14	888	798	655	786	437	454	357	384	235	258	115	196
15	692	790	667	728	307	355	190	313	139	200	118	183
Mean	812.2	836	721.8	818.6	344.4	369.4	274	400.4	176.4	186.6	116.4	150
± SD	105.4	96.7	77.6	112.4	88.3	80.3	89	133	30.3	44.7	25.2	35.9
Δ ± SD (%)	3.2 ± 6.8		13.2 ± 7.3		13.6 ± 37.5		56.4 ± 62.4		7.6 ± 26.8		32.6 ± 36.1	
P value	NS		<0.01		NS		<0.01		NS		<0.01	

AB = after autonomic blockade; BS = basal state; CSRT = corrected sinus node recovery time; F = after flecainide administration; NS = difference not significant; SACT = sinoatrial conduction time; SCL = sinus cycle length; SD = standard deviation.

TABLE II Effects of Flecainide on Atrioventricular Nodal Conduction in the Basal State and After Autonomic Blockade

Pt	A-H (ms)				A_1-H_1 (CL 600 ms)				PCL for WB (ms)				Plasma Level (μg/ml)
	BS	F	AB	AB + F	BS	F	AB	AB + F	BS	F	AB	AB + F	
1	60	70	60	80	—	—	—	90	300	330	310	350	370
2	75	80	75	100	80	85	80	105	310	350	310	370	438
3	60	75	60	75	90	115	70	115	430	460	400	460	336
4	100	120	105	125	115	135	120	160	330	350	370	400	287
5	115	115	100	105	200	195	125	175	430	500	400	460	430
6	95	110	80	105	145	155	90	135	350	370	370	400	402
7	75	100	85	110	100	130	105	155	400	430	400	500	688
8	60	70	60	70	90	90	80	90	350	430	350	400	484
9	100	140	105	145	110	245	110	195	370	540	400	540	341
10	80	80	75	115	110	140	90	145	350	430	370	460	524
11	75	80	75	85	115	115	120	140	460	500	460	540	459
12	105	105	115	125	180	190	170	200	500	540	460	540	350
13	100	105	95	110	110	120	100	130	310	400	330	400	338
14	100	120	95	115	140	180	120	170	500	550	400	500	318
15	70	70	75	85	75	100	85	105	310	370	370	430	347
Mean	84.6	96	84	103.3	118.5	142.5	104.6	144.2	380	436.6	379.9	450	407.4
± SD	18.3	22.4	17.7	21	36.3	45.7	25.8	33.7	69.1	75.3	45	63.4	102.6
Δ ± SD (%)	13.7 ± 12.6		23.7 ± 12.7		22.3 ± 31.5		39 ± 19.3		15.4 ± 11.1		18.2 ± 7		
P value	<0.01		<0.01		<0.01		<0.01		<0.01		<0.01		

A_1-H_1 = A_1-H_1 interval at pacing cycle length of 600 ms; PCL for WB = pacing cycle length for Wenckebach block; other abbreviations as in Table I.

Atrioventricular nodal conduction: Flecainide significantly prolonged A-H interval, A_1-H_1 interval at cycle length of 600 ms (comparable in 14 patients) and pacing cycle length for Wenckebach block both in the basal state (14 ± 13%, $p < 0.01$; 22 ± 32%, $p < 0.01$ and 15 ± 11%, $p < 0.01$, respectively) and after autonomic blockade (+24 ± 13%, $p < 0.01$; 39 ± 19%, $p < 0.01$ and 18 ± 7%, $p < 0.01$, respectively) (Figure 3, Table II). The degree of increase induced by the drug in A-H and A_1-H_1 intervals was significantly more marked after autonomic blockade than in the basal state ($p < 0.01$ and < 0.05, respectively), whereas the degree of change in pacing cycle length for Wenckebach block did not show significant differences. Wenckebach periods occurred in all patients proximal to the His bundle.

The driving cycle length used for the determination of the refractory periods ranged from 550 to 650 ms (mean 603 ± 23). The AV nodal effective and functional refractory periods were comparable only in 3 patients; in the remainder the AV node effective refractory period was shorter than the atrial functional re-

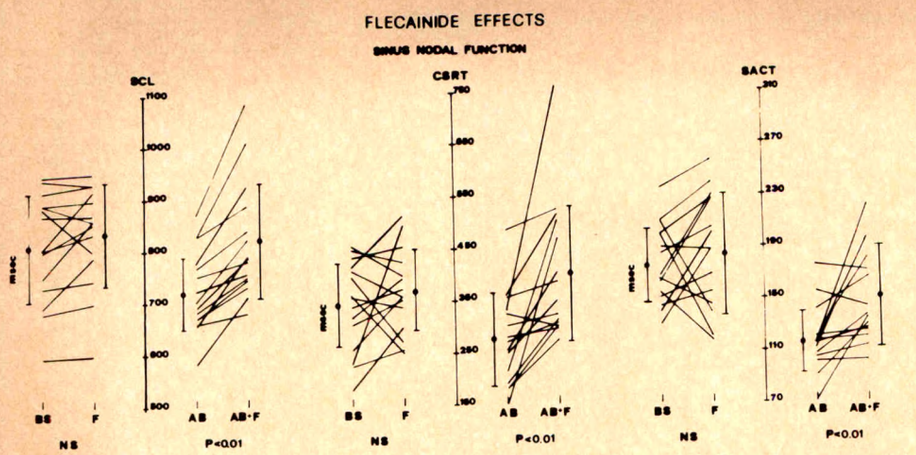

FIGURE 2. The effects of oral flecainide (F) on the electrophysiologic variables of sinus nodal function both in the basal state (BS) and following autonomic blockade (AB) are shown graphically. The means ± standard deviation are represented by the vertical bars on either side. CSRT = corrected sinus node recovery time; SACT = sino-atrial conduction time; SCL = sinus cycle length.

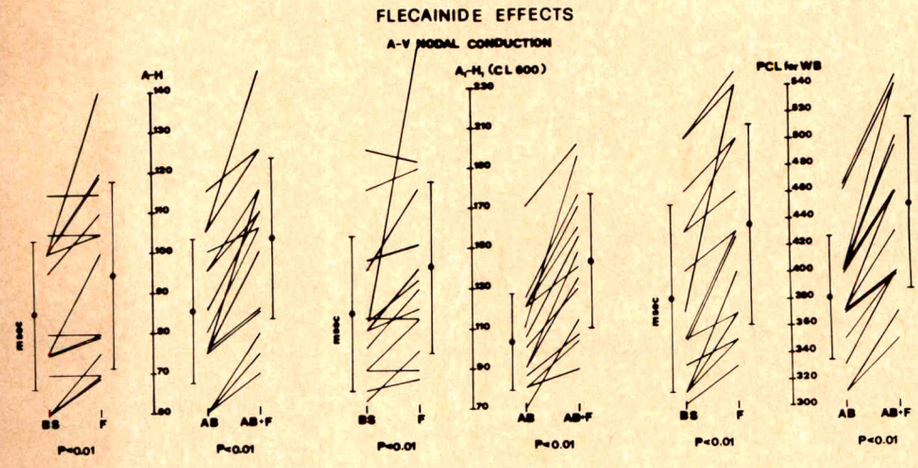

FIGURE 3. The effects of flecainide on the variables of atrioventricular nodal conduction in the basal state and after autonomic blockade. PCL for WB = pacing cycle length for Wenckebach block; other abbreviations as in Figure 2.

fractory period. For this reason, statistical evaluations were not performed.

The H-V and QRS intervals did not change in any patient after autonomic blockade; after flecainide administration, the former increased from a mean of 48 ± 7 to 56 ± 11 ms (percentage increase 16 ± 12%, $p < 0.01$) and the latter from a mean of 107 ± 29 to 121 ± 28 ms (percentage increase: 15 ± 7%, $p < 0.01$).

The plasma flecainide concentrations ranged from 287 to 688 μg/ml (mean 407 ± 103).

In the basal state and after autonomic blockade, flecainide did not change significantly systolic and diastolic pressure.

No major side effects were experienced after either autonomic blockade or flecainide administration. Minor side effects were transient blurring of vision in 1 patient and nausea in another after flecainide, and dryness of the mouth in all patients after autonomic blockade.

Discussion

Oral flecainide was initially prescribed at a daily dosage of 400 to 600 mg. Some investigators[18,19] then suggested that a lower daily dose (200 mg) may be effective, while reducing the incidence of toxicity to a more acceptable level. The electrophysiologic effects of flecainide have been widely investigated after intravenous administration, whereas there are few studies on its effects after oral administration and only at high dosage (300 to 500 mg daily) in patients with supraventricular or ventricular tachycardias.[5–9] In these studies flecainide induced minimal variations in the electrophysiologic variables of sinus node function, whereas it significantly prolonged A-H, H-V and QRS intervals with mean increases over control values of 13 to 39%, 40 to 67% and 14 to 28%, respectively. We administered flecainide at a lower dosage (200 to 250 mg daily) on the basis of these most recent data.

In our study, in the basal state flecainide did not change significantly sinus cycle length, corrected sinus node recovery time and sinoatrial conduction time. It increased significantly the A-H interval by 14% over the control value, A_1-H_1 interval by 22%, pacing cycle length for Wenckebach block by 15%, H-V interval by 16% and QRS complex by 15%. Our results obtained in the basal state are therefore similar to published data,[5–9] with our conduction time increases at the lower end or under the ranges previously reported, very likely due to the lower dose of oral flecainide we administered.

To evaluate the mechanism of action of oral flecainide we used a method previously adopted by us[20–23] and later by Lewis et al.[24] We selected patients with normal sinus rate in the basal state, normal intrinsic

heart rate and normal A-H interval to carry out the investigation in a group of patients with fairly homogeneous sinus and AV nodal functions.

The data obtained after autonomic blockade show that oral flecainide has a direct depressant effect on sinus nodal function and AV nodal conduction: it prolonged all the intrinsic electrophysiologic variables of the 2 nodes. This effect is consistent with the previous findings obtained in cardiac tissue preparations.[1-4] Moreover, our results show that the direct depressant effect of oral flecainide is significantly more marked than the overall effect; in fact the percentage increases in sinus cycle length, corrected sinus node recovery time, A-H and A_1-H_1 intervals were significantly greater after autonomic blockade than in the basal state. This suggests dual actions of flecainide on sinus nodal automaticity and AV nodal conduction in man; one being direct and the other mediated through the autonomic system, which counteracts the first action. Whether the indirect effect is due to a β-adrenergic action or to a vagolytic action is not possible to define in the clinical setting at present. On the basis of experimental data, the former action appears very unlikely, since flecainide partly counteracts the enhanced automaticity induced by isoproterenol in the sinus node of isolated rabbit atria[1] as well as in Purkinje fibers,[4] even if a significant β-blocking effect did not emerge. However, this behavior tends to exclude a β-adrenergic effect, even if it has not been studied specifically. A vagolytic effect of the drug appears more likely also because most class IA antiarrhythmic drugs, such as quinidine, procainamide, diphenylhydantoin and disopyramide,[22,23,25-28] and class IC drugs, such as propafenone and encainide,[21,29] have been shown to have this action.

The overall effects on AV conduction after flecainide alone were more pronounced that those for the sinus node. This suggests that the vagus system has less effect on the AV node compared with the sinus node; hence more depression was evident. This is compatible with previous observations[30,31] showing that the sinus node is more influenced by vagal innervation compared with the AV node.

The effects of flecainide on the parasympathetic system have not been investigated in the experimental setting; this problem warrants more detailed study because a drug with vagolytic action must be administered with caution to patients with glaucoma or urinary retention, particularly in association with other drugs having this autonomic effect. Moreover, our data suggest that flecainide would be expected to have greater clinical impact for patients with sinus node dysfunction or AV nodal conduction disturbances due to its direct negative chronotropic and dromotropic effects. For this reason, the drug should be administered with caution to patients with transplanted hearts that lack vagal innervation.

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Noninvasive Evaluation of Indecainide for Serious Ventricular Tachyarrhythmia

PHILIP J. PODRID, MD, STEPHAN HOHNLOSER, MD, and BERNARD LOWN, MD

Indecainide, a new class 1C agent, was administered to 16 patients with a history of ventricular fibrillation or ventricular tachycardia. Evaluation of drug effect consisted of acute testing with 125 mg followed by a period of maintenance therapy. Efficacy, as evaluated with both ambulatory monitoring and exercise testing, was defined as total elimination of runs of ventricular tachycardia, >90% reduction in couplets and >50% decrease in ventricular premature complex. During acute drug testing 9 of the 16 patients responded to the drug. Four patients did not receive maintenance therapy with indecainide, because of toxic side effects. Of the remaining 12 patients, 7 responded to indecainide based on monitoring, 5 responded judged by exercise testing and 4 when both monitoring and exercise testing were considered. There was no correlation between dose, blood level of drug and effect on arrhythmia. In this small group acute drug testing did not appear to predict the response to the drug during maintenance therapy. Neurologic side effects were reported by 5 patients. Aggravation of arrhythmia occurred in 5 patients, 3 of whom had this complication during acute drug testing and 2 during maintenance therapy. Left ventricular ejection fraction, measured before and during therapy, decreased from an average of 43% to 35% ($p < 0.005$). A reduction was observed irrespective of baseline left ventricular function. Indecainide is an effective antiarrhythmic agent in a small number of highly selected patients with serious ventricular arrhythmia, but potentially serious side effects limit its usefulness.

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Several new antiarrhythmic drugs are now available for treatment of patients with serious ventricular arrhythmia. When evaluated with noninvasive methods each of these agents is effective in only 40 to 60% of patients.[1-4] Furthermore, side effects are frequent. There is need for a highly effective and safe agent for suppressing ventricular arrhythmia and preventing sudden death. Indecainide is a new, potent antiarrhythmic drug.[5] Little data have been reported to date about its efficacy and safety in patients presenting with life-threatening ventricular tachyarrhythmias. The present study reports our experience with indecainide in 16 patients presenting with symptomatic ventricular tachycardia (VT) or ventricular fibrillation (VF) refractory to other antiarrhythmic drugs.

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Dr. Podrid's present address: Section of Cardiology, University Hospital, Boston, Massachusetts.

Address for reprints: Philip Podrid, MD, Lown Cardiovascular Laboratory, 221 Longwood Avenue, Boston, Massachusetts 02115.

Methods

The study population consisted of 16 patients (11 men, 5 women) ages 22 to 76 years (mean 53). Coronary artery disease was present in 7 patients, idiopathic dilated cardiomyopathy in 5 and in 4 no structural disease was documented by cardiac catheterization or echocardiography. Presenting arrhythmia was VF in 4 patients and VT in 12, 9 of whom had sustained VT with hemodynamic instability (syncope or hypotension) and 3 who had runs of nonsustained VT associated with presyncope. In no patient was the arrhythmia the result of an acute myocardial infarction or other precipitating factor. Each patient had been re-

fractory to quinidine, disopyramide and procainamide with documented recurrence of arrhythmia at a time when blood levels were in a defined therapeutic range. An average of 5.5 drugs[3-8] had been ineffective before entry into this study and indecainide was the first investigational drug tested.

The protocol for a noninvasive drug evaluation has been reported previously.[6,7] After admission, antiarrhythmic therapy was withdrawn. Diuretics, digoxin and antianginal medications including β blockers, nitrates and calicum antagonist agents were continued if clinically indicated. After a washout period extending for at least 4 half-lives of the previously administered antiarrhythmic drug, patients underwent baseline studies, including 48 hours of continuous ambulatory monitoring and an exercise test on a motorized treadmill adhering to a Bruce protocol.

Data recorded from each 24-hour ambulatory monitoring period included the total and hourly number of ventricular premature complexes (VPCs), couplets and runs of VT. For the purpose of analysis, the 2 monitor recordings were compared to establish the reproducibility of each form of arrhythmia and the hourly number of each form averaged over the 48 hours. Routine chemistry evaluations and a complete blood count were obtained during this period. Left ventricular ejection fraction was measured by a gated blood pool radionuclide angiogram using technetium-99m pyrophosphate. For patients with a high density of VPCs (>10% of QRS complexes) a list mode format was utilized as previously reported.[8] This permitted the analysis of ejection fraction using only those sinus beats not immediately preceded by a VPC.

At the conclusion of baseline study, the effect of indecainide on arrhythmia was evaluated in 2 ways. Acute drug testing[7,9] involved administration of a single large dose of drug, while short-term maintenance therapy involved multiple doses given during several days of therapy.[6,7] The protocol for acute drug testing has been previously reported.[9,10] On the day of the test, each patient underwent a 30-minute period of continuous electrocardiographic recording by trendscription[11] and a brief period of exercise on a bicycle ergometer. At the conclusion of this baseline period, indecainide (125 mg) was administered orally and monitoring by trendscription continued for 3 hours. Each hour bicycle ergometry was repeated, an electrocardiogram was recorded for measurement of intervals and bloods were drawn for determination of indecainide levels. At the conclusion of the acute drug test, maintenance therapy with indecainide was begun at a dose of 50 mg 3 times daily. After at least 48 hours of therapy the dose could be increased to 75 mg 3 times daily if there were no side effects and if arrhythmia was still present as judged by continuous telemetered monitoring. After an additional 48 hours of therapy the dose could be increased further to a maximum of 100 mg 3 times daily. At the completion of the dosing period, 24-hour ambulatory monitoring, exercise testing on a motorized treadmill and a radionuclide angiogram were repeated. Routine chemistries and an indecainide blood level, drawn 2 hours after a dose, were also obtained.

Criteria for drug efficacy during acute drug testing and short-term maintenance therapy, as evaluated by monitoring and exercise testing, included[6,7]: (1) $\geq$50% reduction in VPCs, (2) $\geq$90% decrease in couplets and (3) total elimination of runs of VT.

Analyses of serum for the levels of indecainide and its metabolite, desisopropyl indecainide, were performed by the sponsoring pharmaceutical company.[12]

Statistical analyses were performed using the Student *t* test for paired and unpaired data and chi square. Data are expressed as mean ± standard error of the mean. Significance was defined as $p < 0.05$.

Results

Control studies: The number of VPCs during the monitoring period was 6,408 ± 1,156 daily (1,620 to 14,939) or 267/hour. When the 2 days were compared, the hourly number of VPCs for each patient was not statistically different and the total number of VPCs was reproducible. Each patient had frequent couplets with an average of 623 ± 216 daily (41 to 1,660). Runs of nonsustained VT, 52 ± 18 (4 to 273) daily, were present in 14 patients. For each patient the number of couplets and runs of VT was reproducibly present during both 24-hour monitoring periods.

During control, the exercise duration was 475 seconds (190 to 1,025 seconds) and the peak sinus rate achieved was 152 beats/min (99 to 200). With exercise 153 ± 29 VPCs were induced. Each patient had frequent couplets, with 16 ± 4 per test. Runs of VT were induced in 13 patients and there were 9 ± 5 runs per test. The average left ventricular ejection fraction was 41% (range 20 to 71%). In 7 patients the ejection frac-

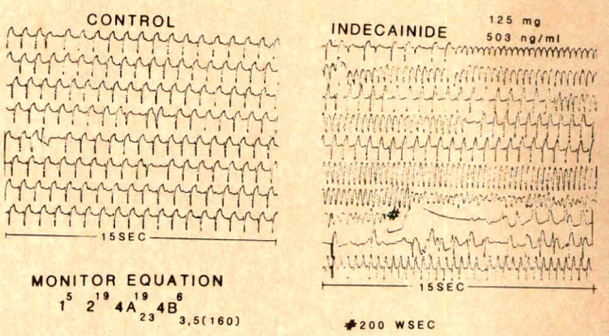

FIGURE 1. Aggravation of arrhythmia during acute drug testing. The patient had a history of sustained ventricular tachycardia. During control monitoring there were 5 hours of grade 1 (1^5) ventricular premature complexes, 19 hours of frequent grade 2 ventricular premature complexes (2^{19}) and 19 hours of couplets with up to 23 episodes/hour ($4A^{19}_{23}$). Nonsustained ventricular tachycardia was present for 6 hours with up to 3 runs/hour, 5 beats in length and at a rate of 160 ($4B^{6}_{3,5(160)}$). Two hours after receiving 125 mg of indecainide and with a blood level of 503 ng/ml, the patient spontaneously developed long runs of ventricular tachycardia and finally went into ventricular fibrillation requiring defibrillation.

tion was >50% (average 62%) while in 9 patients it was <50% (average 23%).

Acute drug test: During acute testing, 9 of the 16 patients (56%) responded to indecainide at 2 hours. The peak indecainide blood level in the responders was 832 ± 120 ng/ml and 44 ± 7 ng/ml for its metabolite, desisopropyl indecainide. In the 6 nonresponders the indecainide and metabolite levels were similar, 631 ± 103 ng/ml and 41 ± 4 ng/ml, respectively (difference not significant). Three patients experienced an aggravation of arrhythmia 2 to 3 hours after receiving indecainide (Figure 1). One patient developed sustained VT with hypotension, which, unlike the clinical VT, could not be reverted with lidocaine or cardioversion. After 6 hours of sustained VT with dopamine support for maintenance of blood pressure, he was cardioverted. Two patients developed VF for the first time. The blood levels of indecainide and its metabolite at the time of aggravation were 578, 884 and 503 ng/ml (average 655) and 34, 59 and 42 ng/ml (average 45), respectively. These were not significantly different from the levels in patients who did not exhibit aggravation. There were no associated QRS or QT interval changes in these 3 patients.

Short-term maintenance therapy: Twelve patients underwent repeat ambulatory monitoring while receiving indecainide therapy; 4 others were excluded, 3 with aggravation of arrhythmia during acute drug testing and 1 patient who developed severe neurologic side effects after 2 days of therapy with indecainide

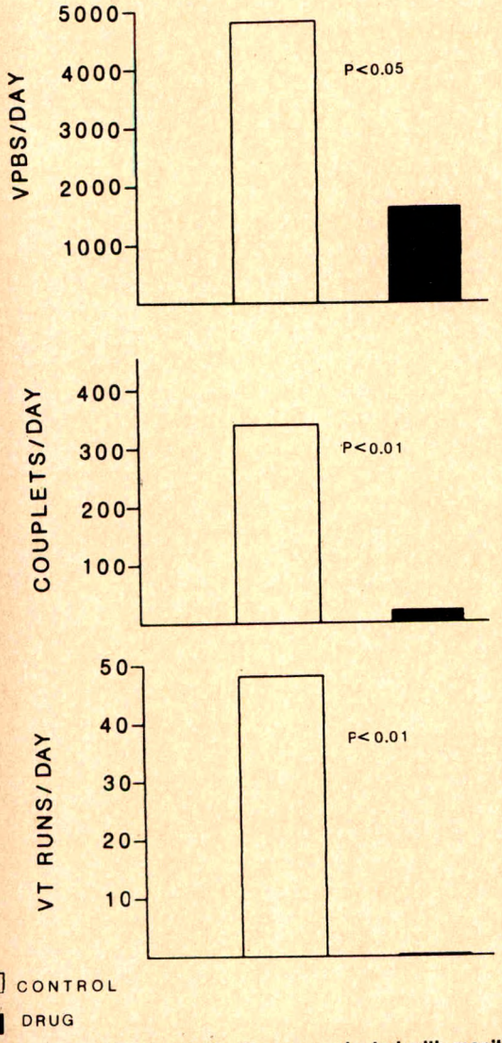

FIGURE 2. Results of indecainide therapy evaluated with monitoring. Among the 7 patients who responded to indecainide, ventricular premature beats (VPBs) per day were reduced by 67% from 4,814 to 1,624 ($p < 0.05$), couplets were reduced by 95% (334 to 18, $p < 0.01$). Runs of ventricular tachycardia (VT) (47/day) were eliminated ($p < 0.01$).

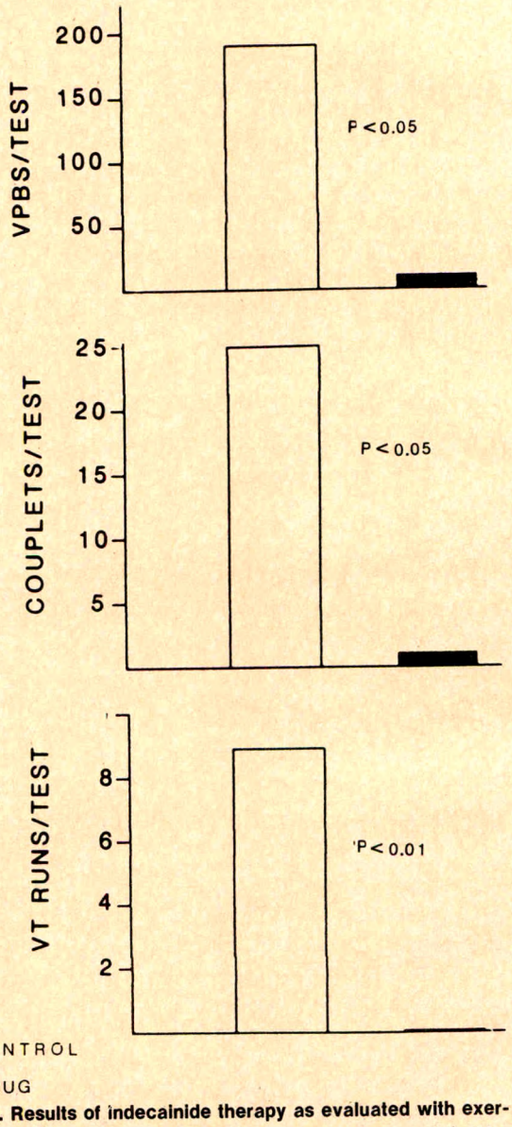

FIGURE 3. Results of indecainide therapy as evaluated with exercise testing. In the 5 patients who responded, the number of ventricular premature beats (VPBs) decreased from 189 to 23 per test or 88% ($p < 0.05$). Couplets were reduced from 25 to 2 per test (92%, $p < 0.05$) while runs of ventricular tachycardia (VT) were eliminated ($p < 0.05$).

150 mg daily. Based on criteria, 7 patients (58%) responded to indecainide as evaluated with monitoring. Daily VPCs decreased from 4,814 to 1,624 (67%, $p < 0.05$), couplets were reduced by 95%, from 334 to 18 daily ($p < 0.01$) (Figure 2) and runs of VT (average 47 daily) were eliminated ($p < 0.01$). Among the 5 nonresponders, there was no statistically significant change in daily VPCs (10,088 vs 10,346) couplets (701 vs 241) or runs of VT (87 vs 70).

Five of 13 patients (38%) showed a response to indecainide with exercise testing. In the responders the number of VPCs per test was reduced from 189 to 23 (88%, $p < 0.05$), couplets decreased from 25 to 2 per test (92%, $p < 0.05$), while runs of VT were eliminated ($p < 0.01$) (Figure 3). Exercise test duration was not significantly different (452 vs 497 seconds, difference not significant). Among the 8 nonresponders there was no significant change in exercise test duration and no significant change in frequency of VPCs, couplets or runs of VT.

When assessment of efficacy was based on the results of monitoring and exercise testing, 4 of the 16 patients originally entered (25%) responded to indecainide (Figure 4). The daily dose used was 150 mg in 4, 225 mg in 7 and 300 mg in 1. The average blood levels of drug and metabolite were 346 and 81 μg/ml, respectively, in responders compared with 448 and 78 μg/ml in the nonresponders (difference not significant).

Comparison between acute and maintenance therapy: Acute drug testing and short-term maintenance therapy was completed by 12 patients (Figure 5). All 4 patients who responded during maintenance therapy responded acutely. Of the 3 patients who did not respond acutely indecainide was ineffective in each. Therefore, 7 of 12 patients (58%) had concordant responses, but in this small group this was not statistically significant (difference not significant).

Blood levels of indecainide achieved acutely were significantly higher than those during maintenance (752 vs 417 ng/ml, $p < 0.005$). In the 7 patients who had concordant results, the average indecainide blood level was higher during the acute drug test (Table I). The average level of metabolite was higher during maintenance therapy. The same relation was observed in the 5 patients with a discordant response.

Left ventricular function: The average left ventricular ejection fraction during baseline in the 12 patients who completed the protocol was 43 ± 7% and was reduced to 35 ± 5% during indecainide therapy ($p < 0.005$) (Table II). Both responders and nonresponders had a similar decrease in ejection fraction during drug therapy. In 6 patients with normal ventricular function (≥50%), the drug reduced the ejection fraction from 62 to 49% ($p < 0.01$) and in the 6 with impaired function it was reduced from 24 to 21% ($p < 0.01$).

Side effects: The most common noncardiac side effects were neurologic. Lightheadeness was reported by 4 patients while 1 patient experienced confusion and thought disorders. In 3 patients there was nondose-related, marked QRS widening. Blood levels were not significantly different in those with side effects compared to those without toxic effects. Aggravation of arrhythmia was observed in 5 patients (31%). In 3 exacerbation of arrhythmia occurred during acute drug testing. One patient who received 150 mg daily for 4 days developed sustained VT for the first time on the treadmill. The fifth patient only had nonsustained VT during exercise, while with indecainide therapy he developed nonsustained VT during ambulatory monitoring and sustained VT during exercise testing. In

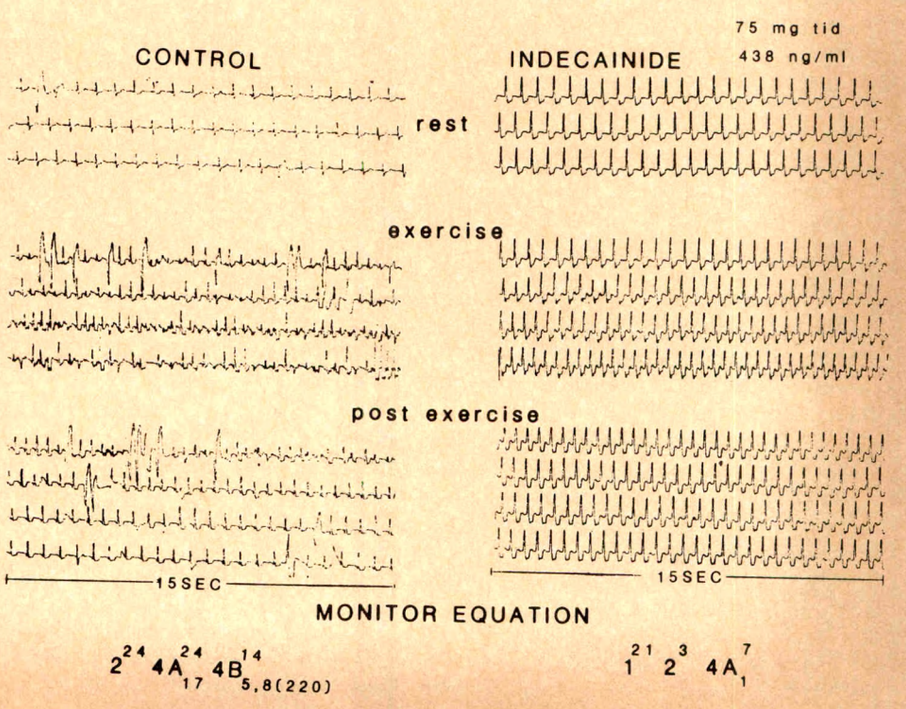

FIGURE 4. Responder to indecainide. In control the patient had frequent ventricular premature beats, couplets and runs of ventricular tachycardia induced by exercise. Ambulatory monitoring demonstrated 24 hours of frequent (>30/hour) ventricular premature complexes (2^{24}), 24 hours of couplets with as many as 17/hour ($4A^{24}_{17}$) and 14 hours of ventricular tachycardia. There were as many as 5 runs/hour, 8 beats in length at a rate of 220 ($4B^{14}_{5,8(220)}$). During indecainide therapy marked QRS widening occurred. Arrhythmia with exercise was eliminated, while ambulatory monitoring demonstrated 21 hours of infrequent (<30/hour) ventricular premature complexes, 3 hours of frequent ventricular premature complexes (2^{3}) and 7 couplets during the day ($4A^{7}_{1}$).

TABLE I Blood Levels

	Drug (ng/ml)	Metabolite (ng/ml)	p Value
Acute drug test			
Responders (n = 9)	832	44	
Nonresponders (n = 6)	631	41	NS
Aggravators (n = 3)	655	45	
Short-term maintenance			
Responders (n = 4)	346	81	NS
Nonresponders (n = 8)	448	78	
Acute maintenance			
Concordancy (n = 7)	846/431	50/85	NS
Discordancy (n = 5)	753/409	32/60	

NS = difference not significant.

TABLE II Effect of Indecainide on Left Ventricular Function

		Ejection Fraction		
	No.	Control (%)	Drug (%)	p Value
Overall	12	43	35	<0.005
Responders	4	45	38	<0.05
Nonresponders	8	41	34	<0.05
EF >50%	6	62	49	<0.01
EF <50%	6	24	21	<0.01

EF = ejection fraction.

these 2 patients indecainide had been ineffective during acute drug testing. The blood levels of indecainide and its metabolite were similar to those of patients who did not have aggravation.

Discussion

Indecainide is similar to other membrane-active drugs because it reduces the maximum rate of increase in phase 0 of the action potential and decreases conduction velocity through the myocardium.[13] There is a slow rate of tissue repolarization. The drug has little effect on the effective refractory period of the myocardium. In the canine Purkinje fiber, the drug shortens the action potential duration, while it lengthens it within the ventricular muscle.[13] These features are typical for drugs within the 1C subclass of antiarrhythmic agents, which include encainide[14] and flecainide.[15] Indecainide has no effect on sinus node automaticity or the slope of phase 4 of Purkinje fibers in the ventricle.[13,16] In the atrium, the drug shortens action potential duration, but has little effect on the refractory periods.[13]

There are only a few studies involving indecainide therapy in humans. Horowitz et al[5] administered intravenous drug to 10 patients with inducible VT. At a dose of up to 90 mg/kg, there was no effect on sinus node function or the refractory periods of the atrial and ventricular myocardium. The drug did significantly slow conduction through the atrioventricular node and His Purkinje tissue, but prolonged the AH, HV and QRS intervals, similar to the effects of encainide and flecainide.[14,15] Only 1 patient was rendered noninducible after intravenous indecainide therapy. However, similar to encainide[17] and flecainide,[18] the drug did significantly prolong the VT cycle length from 248 to 320 ms ($p < 0.001$).

In a study by Morganroth et al,[19] 14 patients with frequent VPCs and nonsustained VT received 150 to 300 mg of indecainide daily. In 11 patients (85%) VPCs were reduced by 90%, and in 12 patients (86%) VT was eliminated. Similar results were reported by Krejci,[20] Siddoway[21] and their co-workers. In a comparative study with disopyramide involving 231 patients, indecainide reduced VPCs by 93% while with disopyramide there was an 80% decrease in VPCs ($p < 0.05$).[22] However, the 2 drugs were of equivalent efficacy for the suppression of runs of VT.

Data about the effect of indecainide on spontaneous arrhythmia in patients with a history of sustained tachyarrhythmias are lacking. In the present study indecainide significantly reduced the frequency of VPCs, couplets and eliminated VT in 7 patients as evaluated with monitoring and in 5 of 13 patients based on exercise. When both monitoring and exercise testing were considered, only 4 of the 16 patients (25%) responded to indecainide.

In this small group indecainide was less effective when compared with other investigational drugs evaluated with the same protocol in patients with life-threatening ventricular arrhythmia refractory to conventional agents.[1-4] As with other drugs, no correlation was noted between drug efficacy and the dose used, the serum blood level achieved or changes on the electrocardiogram.

An important concern is the ability to predict drug effect. In our experience with quinidine,[9] mexiletine[2] and propafenone,[3] acute drug testing is predictive of the response to maintenance therapy, with an 80 to 88% concordancy. Acute drug testing with indecainide did not appear to correlate with the effect of maintenance therapy, although it does appear that failure to respond acutely will predict inefficacy of the drug

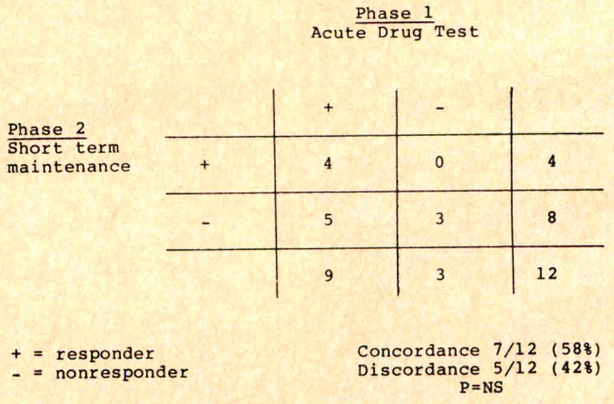

FIGURE 5. Correlation between phase 1 and phase 2 studies. Of the 12 patients undergoing acute drug testing and maintenance therapy with indecainide, (58%) had concordant results, while 5 (42%) who responded to the drug acutely did not respond during maintenance therapy. NS = difference not significant.

when given on a long-term basis. However, the number of patients is small. Studies involving more patients are necessary to better define this relation. The discordance may be related to higher peak indecainide levels during acute drug testing compared with maintenance therapy (752 vs 417 μg/ml).

Worrisome are the side effects we encountered. In this study indecainide only infrequently produced neurologic symptoms, similar to the comparative study of Morganroth et al.[22] Of particular concern is cardiac toxicity. In our patients, indecainide significantly reduced the left ventricular ejection fraction in 9 of 12 patients, although no patient developed signs or symptoms of failure, perhaps because of a brief period of dosing. Of even greater concern is the drug-induced aggravation of arrhythmia. This complication has been reported to occur in 11% of antiarrhythmic drug studies[23,24] and especially in patients with a history of sustained ventricular tachyarrhythmia.[23,25] In the study of Morganroth et al,[22] aggravation of arrhythmia was observed in 12 of 114 patients (11%) receiving indecainide. In the present studies, indecainide aggravated arrhythmia in 5 of 16 patients (31%). There were no electrocardiographic changes associated with aggravation and blood levels were similar to those achieved in patients without this complication. As with other drugs, this life-threatening complication urges cautious use of indecainide, especially in patients with a history of sustained VT or VF with impaired left ventricular function.

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Coupling Intervals of Ventricular Extrastimuli Causing Resetting of Sustained Ventricular Tachycardia Secondary to Coronary Artery Disease: Relation to Subsequent Termination

MARK E. ROSENTHAL, MD, NICHOLAS J. STAMATO, MD, JESUS M. ALMENDRAL, MD, CHARLES D. GOTTLIEB, MD, and MARK E. JOSEPHSON, MD

Single and double ventricular extrastimuli (VE) delivered during sustained, uniform ventricular tachycardia (VT) are able to reset or terminate the tachycardia. The relation between the coupling intervals of single and double VE resetting VT and those terminating it was examined in 80 uniform, morphologically distinct VT occurring in 52 patients. Of the 80 tachycardias receiving single VE, 41 were reset and 8 terminated. The corrected coupling interval of single VE first causing resetting was 0.81 ± 0.08 compared with 0.66 ± 0.06 for termination ($p < 0.001$). Forty-two tachycardias received double VE with 33 being reset and 13 terminating. The corrected coupling interval of double VE at which resetting was first seen was 0.86 ± 0.08 compared with 0.73 ± 0.05 for termination ($p < 0.001$). If the longest corrected coupling interval causing resetting was ≥0.75, then 7 of 34 tachycardias terminated with single VE and 13 of 31 terminated with double VE compared with only 1 of 46 terminating with single VE and 0 of 10 with double VE if resetting was not observed by a corrected coupling interval of 0.75 ($p < 0.01$ and $p < 0.02$, respectively). If the longest corrected coupling interval at which resetting occurred was ≥0.75, the predictive value for VT termination was 21% with single VE and 42% with double VE compared with only 2% with single VE and none with double VE if resetting was not observed by this corrected coupling interval. Thus, critical coupling intervals can be identified during the delivery of premature extrastimuli where if resetting has not occurred, termination is unlikely. Potential applications of these findings in algorithms for antitachycardia pacemakers exist.

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Programmed ventricular extrastimuli delivered during sustained, uniform ventricular tachycardia (VT) may reach the site of tachycardia origin and cause resetting or termination of the rhythm.[1,2] The ability of different modalities of programmed ventricular stimulation to terminate VT has been evaluated and incorporated into protocols for tachycardia termination, both in the electrophysiology laboratory and in chronically implanted antitachycardia devices.[3–16]

We and others have shown that resetting or entrainment (i.e., continuous resetting) of VT may be demonstrated before termination as increasingly premature ventricular extrastimuli (VE) are delivered or incremental ventricular pacing is performed during VT.[2,12–14] The present study expands our prior observations and examines the relation between the coupling intervals of single and double VE that reset sustained VT and those that terminate it. Potential applications of these findings for the development of more efficient algorithms for the delivery of single or double extrastimuli in antitachycardia devices are discussed.

Methods

Study population: Eighty uniform, morphologically distinct VTs occurring in 52 patients with prior myo-

From the Clinical Electrophysiology Laboratory, Hospital of the University of Pennsylvania, Cardiovascular Section, and Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. This study was supported in part by grants HL28093 and HL07346 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland, and grants from the American Heart Association, Southeastern Pennsylvania Chapter, Philadelphia. Dr. Josephson is the Robinette Foundation Professor of Medicine (Cardiovascular Diseases), University of Pennsylvania School of Medicine. Manuscript received April 6, 1987; revised manuscript received November 17, 1987, and accepted November 22.

Dr. Almendral's current address: Servicio de Cardiologia, Hospital Provincial, Madrid, Spain.

Address for reprints: Mark E. Josephson, MD, Cardiovascular Section, Hospital of the University of Pennsylvania, 3400 Spruce Street, Room 658 Ravdin, Philadelphia, Pennsylvania 19104.

cardial infarction were included for analysis. The patient population was 49 men and 3 women with a mean age of 60.5 ± 9.5 years.

All 80 tachycardias were either directly induced by programmed electrical stimulation or resulted from stimulation during previously induced VT. The mean cycle length of the tachycardias studied was 365 ± 58 ms and all were hemodynamically well tolerated. The tachycardia cycle length was required to be stable over 20 consecutive beats, not varying by more than 20 ms. Fifty-nine tachycardias were studied while the patient was receiving antiarrhythmic therapy while 21 were studied with the patient withdrawn from all antiarrhythmic agents.

Electrophysiologic studies: Electrophysiologic studies were performed in the postabsorptive state following the percutaneous insertion of 1 to 5 quadripolar electrode catheters with 5-mm interelectrode spacing. Programmed stimulation was performed with a custom-designed programmable stimulator (Bloom Associates, Ltd.) that delivered bipolar, rectangular 1-ms pulses at twice the diastolic threshold. Data obtained during the procedure were displayed on a multichannel oscilloscope (Electronics for Medicine VR-16) and recorded with an ink jet recorder (Siemens Elema, Mingograph) at paper speeds of 100, 200, and 250 mm/s and simultaneously recorded on magnetic tape. Surface electrocardiographic leads I, aVF and V_1 were recorded with intracardiac electrograms that were filtered between 30 and 500 Hz. Previously described stimulation techniques, using 1 to 3 VE and rapid ventricular pacing, were used to initiate VT.[6,17]

Delivery of extrastimuli during ventricular tachycardia: Premature extrastimuli delivered during VT were given at the right ventricular apex at twice the diastolic threshold. Single VE (S_1) were introduced in all 80 VT with an initial coupling interval to the prior tachycardia beat (V) equal to 20 ms less than the tachycardia cycle length. S_1 was delivered with increasing prematurity with the V-S_1 interval decreased by 10-ms intervals until 1 of 3 outcomes occurred. First, ventricular refractoriness at the pacing site was reached; second, a sustained change (lasting >30 seconds) in the tachycardia cycle length or morphology occurred or third, termination was observed. Double VE were delivered during 41 VT in the following fashion: the coupling interval of S_1 was fixed so that it did not cause resetting of the VT. This was done by setting the V-S_1 interval 20 ms greater than the longest coupling interval at which resetting occurred, or 20 ms beyond the effective refractory period at the pacing site during VT if resetting was not observed during the introduction of single VE. The second VE (S_2) was then delivered with increasing prematurity, beginning at an S_1-S_2 interval equal to the tachycardia cycle length. S_1S_2 was then decreased by 10-ms intervals until one of the previously described endpoints was reached.The V-S_1 interval remained fixed and therefore only S_2 was allowed to interact with the site of tachycardia origin.

The complete stimulation protocol was not performed during all VT if the patient became hemodynamically unstable during the pacing protocol, if a new morphology of VT was initiated during the introduction of premature extrastimuli or if the VT terminated.

Single and double VE were delivered at least twice at each coupling interval to document reproducibility. When termination occurred, VT was generally not reinitiated to systematically assess the reproducibility of termination nor was a tachycardia termination window defined.

Measurements and definitions: Intervals were measured between the rapid deflections of intracardiac electrograms recorded at the site of pacing.

Resetting of VT with single or double VE occurred if: the pause following ventricular premature extrastimulation was less than fully compensatory by at least 20 ms and the same morphology of VT resumed immediately after premature stimulation with no significant change (<20 ms) from the original tachycardia cycle length.

Acceleration of VT was defined as occurring if there was at least a 20-ms decrease in tachycardia cycle length, after premature stimulation, which was sustained. Changes in the tachycardia QRS morphology concomitant with acceleration were noted.

The coupling intervals for single and double VE were corrected for tachycardia cycle length in the following manner. Corrected coupling interval for single VE = V-S_1 interval/VT cycle length. Corrected coupling interval for double VE = V-S_2 interval/2(VT cycle length).

Statistical analysis: Continuous variables were expressed as the mean ± standard deviation and compared using the unpaired *t* test. Categorical variables were compared using the chi square test.

Results

Single ventricular extrastimuli: Eight of 80 tachycardias (10%) were terminated with single VE while 41 (53%) were reset. Seven of 8 tachycardias were reset at longer V-S_1 coupling intervals before termination. The mean corrected coupling interval of single VE that initially reset VT was 0.81 ± 0.08 compared with a mean corrected coupling interval of 0.66 ± 0.06 that terminated VT ($p < 0.001$). There was no significant difference between the shortest coupling intervals of single VE which captured during those tachycardias that terminated and those that did not. An example of resetting and subsequent termination of the same VT by increasingly premature single VE is shown in Figure 1.

One tachycardia was accelerated during the delivery of single VE without a change in QRS morphology. Six VTs changed morphology after premature stimulation, 4 of which were more rapid than the baseline tachycardia, for an overall incidence of stimulation-induced acceleration of 6.3%. In no instance was degeneration to ventricular fibrillation observed.

Double ventricular extrastimuli: Double VE were delivered during 41 VTs. Thirty-three (80%) were reset and 13 (32%) were subsequently terminated. Twelve of 13 tachycardias were first reset with V-S_2 coupling intervals that exceeded the V-S_2 intervals at which termination was observed. The mean corrected coupling interval at which double VE initially reset VT

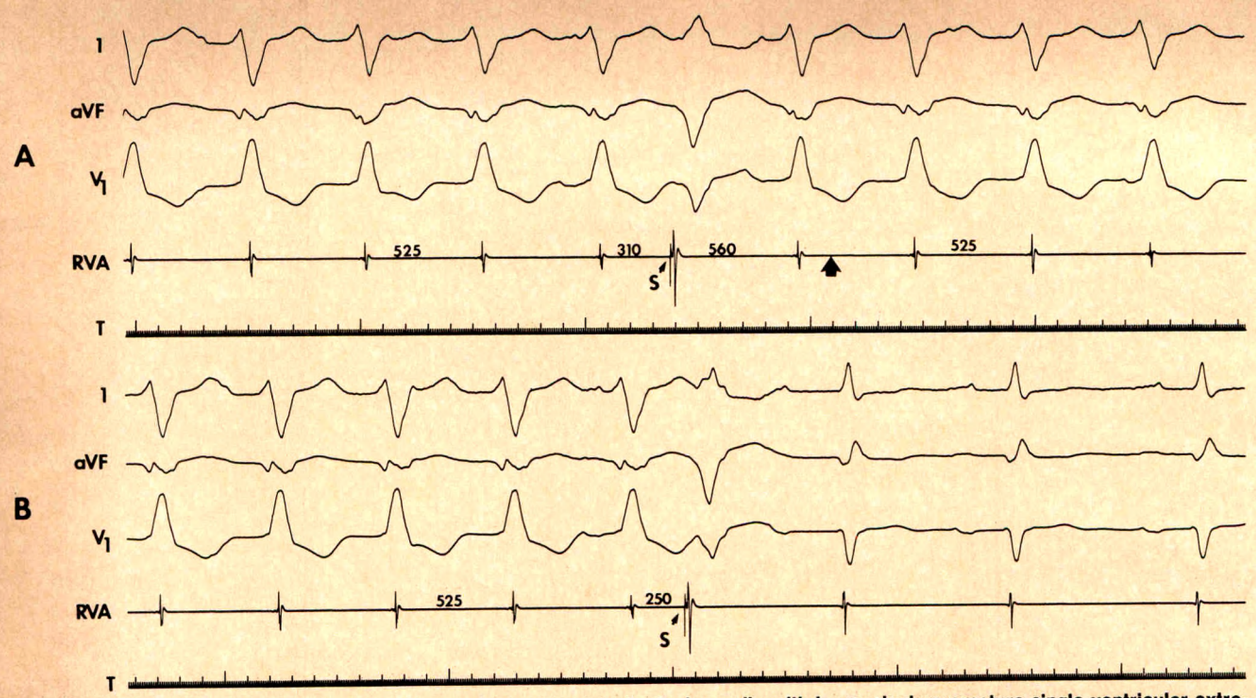

FIGURE 1. Resetting and termination of uniform, sustained ventricular tachycardia with increasingly premature single ventricular extrastimuli. Surface electrocardiographic leads I, aVF and V_1 are displayed with an intracardiac recording from the right ventricular apex (RVA). In *A*, a single ventricular extrastimulus (S) is delivered with a coupling interval to the prior tachycardia beat of 310 ms. The resulting pause of 560 ms, measured at the RVA, is less than fully compensatory; the tachycardia is therefore reset. The *bold upright arrow* indicates where a fully compensatory right ventricular apical electrogram would occur. Note that after premature extrastimuli, the tachycardia resumes without a change in morphology or cycle length. In *B*, a single extrastimulus (S) delivered at the RVA with a coupling interval of 250 ms terminates the tachycardia. T = time lines.

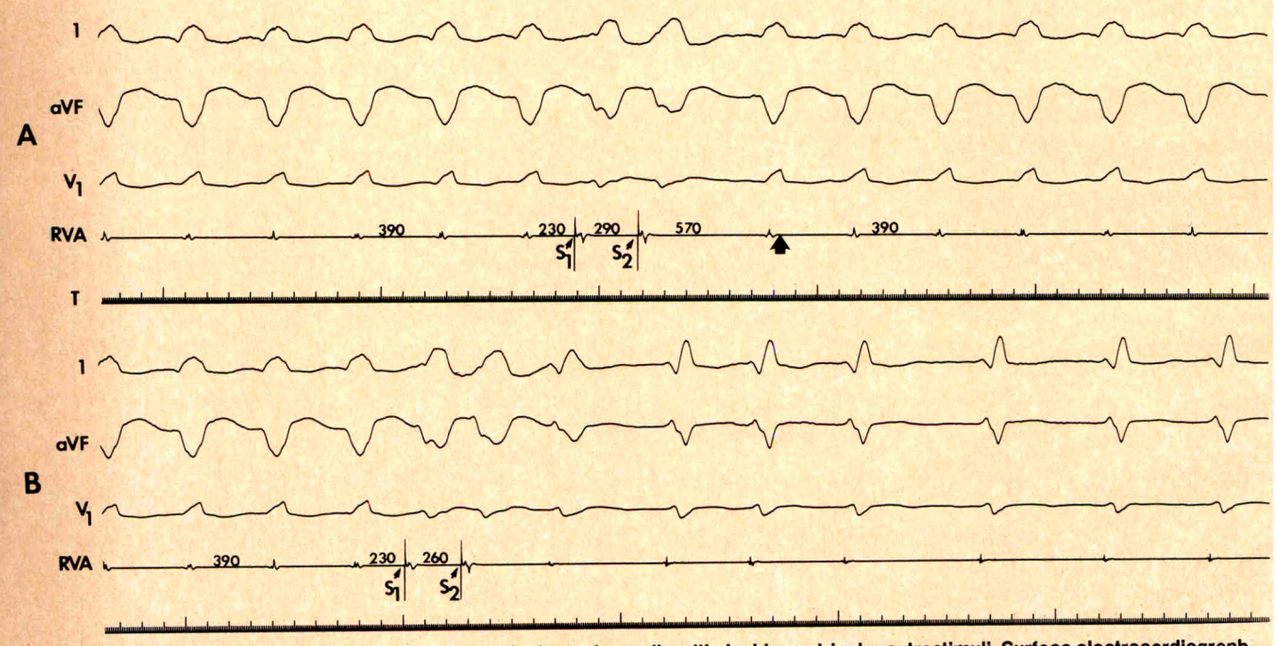

FIGURE 2. Resetting and termination of sustained ventricular tachycardia with double ventricular extrastimuli. Surface electrocardiographic leads I, aVF and V_1 as well as an intracardiac recording from the right ventricular apex (RVA) are displayed. Single extrastimuli did not reset this tachycardia and therefore the coupling interval of the first extrastimulus (S_1) is set at 230 ms, 20 ms greater than the effective refractory period during ventricular tachycardia. In *A*, the interval between S_1 and the second extrastimulus (S_2) was set at 290 ms and resulted in a pause of 570 ms. This is less than fully compensatory (*bold arrow* demonstrates the timing of a fully compensatory electrogram) and therefore the tachycardia is reset. In *B*, the S_1-S_2 interval is 260 ms and termination of ventricular tachycardia occurs with the resumption of the baseline rhythm, atrial fibrillation. T = time lines.

was 0.86 ± 0.08 compared with a mean corrected coupling interval of 0.73 ± 0.05 for tachycardia termination ($p < 0.001$). An example of resetting and later termination of the same VT with double VE is shown in Figure 2.

No tachycardias were accelerated without a change in QRS morphology. Five tachycardias changed morphology after double VE with a decrease in the tachycardia cycle length in 2. The overall incidence of tachycardia acceleration was 4.9%. Degeneration to ventricular fibrillation was not seen.

Use of resetting to identify tachycardias that terminated: Because resetting of VT preceded termination in 90% of the tachycardias that were terminated, a corrected coupling interval at which tachycardia resetting was first observed was sought to identify tachycardias that would subsequently be terminated. For single VE, if resetting was first observed at a V-S_1 interval ≥75% of the tachycardia cycle length (corrected coupling interval ≥0.75), then 7 of 34 tachycardias were terminated compared with only 1 of 46 tachycardias when resetting was not observed by a corrected coupling interval of 0.75 ($p < 0.01$). For double VE, if the corrected coupling interval at which resetting was first observed was ≥0.75, then 13 of 31 tachycardias terminated compared with 0 of 10 tachycardias that terminated if resetting was not observed by a corrected coupling interval of 0.75 ($p < 0.02$). Using a value of 0.75, the predictive value for tachycardia termination was 21% for single VE and 42% for double VE if resetting was first observed at coupling intervals above this value. If resetting was not observed by a corrected coupling interval equal to 0.75, the predictive value for tachycardia termination was 2% for single VE and 0% for double VE (Table I).

TABLE I Relation Between Longest Corrected Coupling Interval Causing Resetting and Subsequent Termination

	Longest Corrected Coupling Interval Causing Resetting ≥0.75	
	SVE	DVE
Predictive value for termination	19%	42%
	<0.75	
Predictive value for no termination	98%	92%

DVE = double ventricular extrastimuli; SVE = single ventricular extrastimuli.

Discussion

Programmed ventricular extrastimuli have been shown to be efficacious for the termination of sustained, uniform VT.[2,6,9-16] Previous reports have demonstrated single VE to be effective in terminating VT in up to 53% of patients, with 8 to 48% of tachycardia episodes being successfully terminated.[2,6,9-16] In these studies, double VE terminated VT in up to 75% of patients with 11 to 58% of tachycardia episodes being terminated.[2,6,9-16] Both of these pacing modalities have been shown to be inferior to bursts of rapid ventricular pacing for tachycardia termination.[2,6,9-15] However, they are generally considered to be safer in that the incidence of VT acceleration or degeneration to ventricular fibrillation is less common with these modalities than with bursts of rapid ventricular pacing.[3,4,7-9] Therefore, some means to "screen" for potential efficacy of single and double VE for tachycardia termination early in their delivery would be useful in identifying tachycardias that require more aggressive pacing methods.

This report is the first to examine the potential role for the resetting response in algorithms for pacing termination of VT. Previously, termination of sustained VT has been shown to be preceded by entrainment during incremental ventricular pacing.[2,12-14] Similarly, resetting of VT was demonstrated before termination during the delivery of increasingly premature single and double VE.[2]

This study extends these observations by analyzing the coupling intervals with which single and double VE first reset and subsequently terminate VT.

As diastole was scanned with increasingly premature VE, the incidence of tachycardia termination with a single extrastimulus was 21% if resetting was first observed with a coupling interval ≥75% of the tachycardia cycle length, and only 2% if resetting was not observed by this coupling interval. Similarly, as diastole was scanned with the second of 2 VE, the incidence of termination was 42% if resetting was observed by a corrected coupling interval of 0.75, and 0% if resetting was not observed by this coupling interval.

The findings of this study have potential utility in automatic, adaptive, antitachycardia pacemakers. Such a device could detect tachycardia resetting by monitoring the return cycle at the pacing site following premature extrastimulation. If resetting was not detected with single VE by a coupling interval equal to 75% of the tachycardia cycle length, then the unit could automatically shift to the delivery of double VE as the next pacing modality. The V-S_1 interval would automatically be set at a predetermined percentage of the tachycardia cycle length determined during baseline electrophysiologic testing and diastole would be scanned with S_2. If resetting was observed in either instance by a corrected coupling interval ≥0.75, the remainder of diastole would be scanned until either termination occurred or refractoriness was reached before resorting to a more aggressive mode of pacing. In this way, these safer but less efficacious pacing modalities could be more efficiently used.

Theoretical considerations: The tachycardias included in this study were all the result of programmed electrical stimulation, with the vast majority occurring in patients with coronary artery disease. The underlying mechanism of VT in this setting is thought to be due to reentry.[1,6] Resetting of reentrant VT occurs when a premature extrastimulus is able to enter the circuit, collide with the prior orthodromic wavefront retrogradely and propagate antegradely over the excitable gap to exit the circuit early (Figure 3). Termination may occur when a sufficiently premature extrastimulus results in block in both limbs of the circuit, extinguishing

the tachycardia (Figure 3). This study demonstrates that early penetration of programmed extrastimuli into the circuit, indicated by resetting of VT, is usually a prerequisite for subsequent termination.

Limitations and conclusions: The VT included in this study were all uniform, hemodynamically well tolerated and with a stable cycle length. The findings cannot be extended beyond this subgroup. However, it is this specific group of tachycardias in which antitachycardia pacing would be applied.

The method in which premature VE were delivered could have influenced the success rate for tachycardia termination. Ventricular extrastimuli were delivered at twice diastolic threshold. Since increased current strength has been shown to facilitate tachycardia termination,[18] the use of higher currents might have increased the incidence of termination. It is also possible that a more closely coupled S_1 during the delivery of double VE might have led to maximal "peeling back" of intervening tissue refractoriness and easier access to the circuit with a greater incidence of termination. In this study, only S_2 interacted with the tachycardia circuit and comparison with extrastimulus techniques in which S_1 was made more premature during the delivery of double extrastimuli is not possible.

This study demonstrates that resetting of VT with single and double VE usually occurs at longer extrastimulus coupling intervals than termination. As increasingly premature extrastimuli are used to scan diastole, a critical coupling interval can be identified where if resetting has not occurred, termination is unlikely. This finding has potential applications in the development of more efficient uses of single and double VE in antitachycardia pacemakers capable of adaptive pacing modalities.

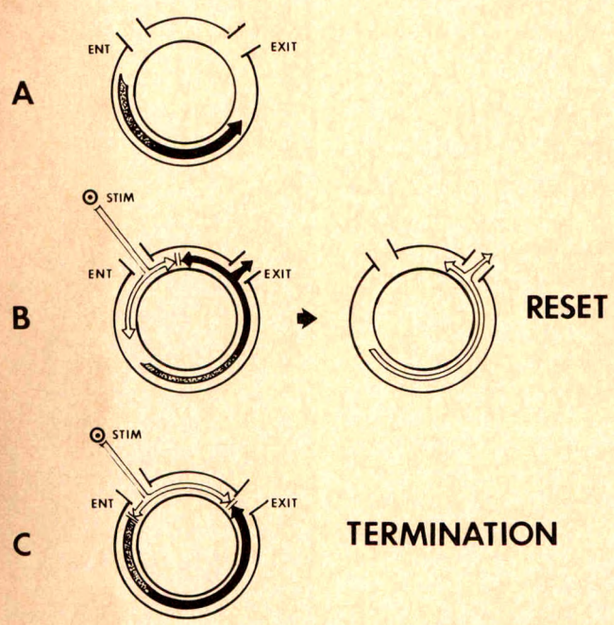

FIGURE 3. In *A*, a schematic representation of the reentrant circuit is illustrated with separate entrance (ent) and exit sites. During ventricular tachycardia, a wavefront is shown propagating through the tissue of the reentrant circuit (*arrow*). The *black portion* of the arrow represents fully refractory tissue while the *dotted portion* represents partially refractory tissue. In *B*, a premature ventricular stimulus (stim) introduced during the tachycardia results in a wavefront of depolarization (*open arrow*), which enters the reentrant circuit and conducts antegradely over fully excitable tissue while it collides retrogradely with the already propagating wavefront (*black and dotted arrow*). The premature wavefront (*open arrow*) then propagates around the circuit to the exit site, leading to the less than compensatory pause and resetting of the tachycardia. In *C*, a more premature ventricular extrastimulus (stim) results in a wavefront of depolarization (*open arrow*), which enters the circuit at a time when it collides retrogradely with the previously propagating wavefront (*black and dotted arrow*) and encounters antegrade tissue incapable of sustaining further propagation. As a result, circus movement in the circuit is extinguished and tachycardia terminates.

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CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia.

WARNINGS: The NITRO-DUR system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

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Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NITRO-DUR is administered to a nursing woman.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing NITRO-DUR therapy. If headache persists, the NITRO-DUR dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the NITRO-DUR dosage should be reduced or use of the product discontinued.

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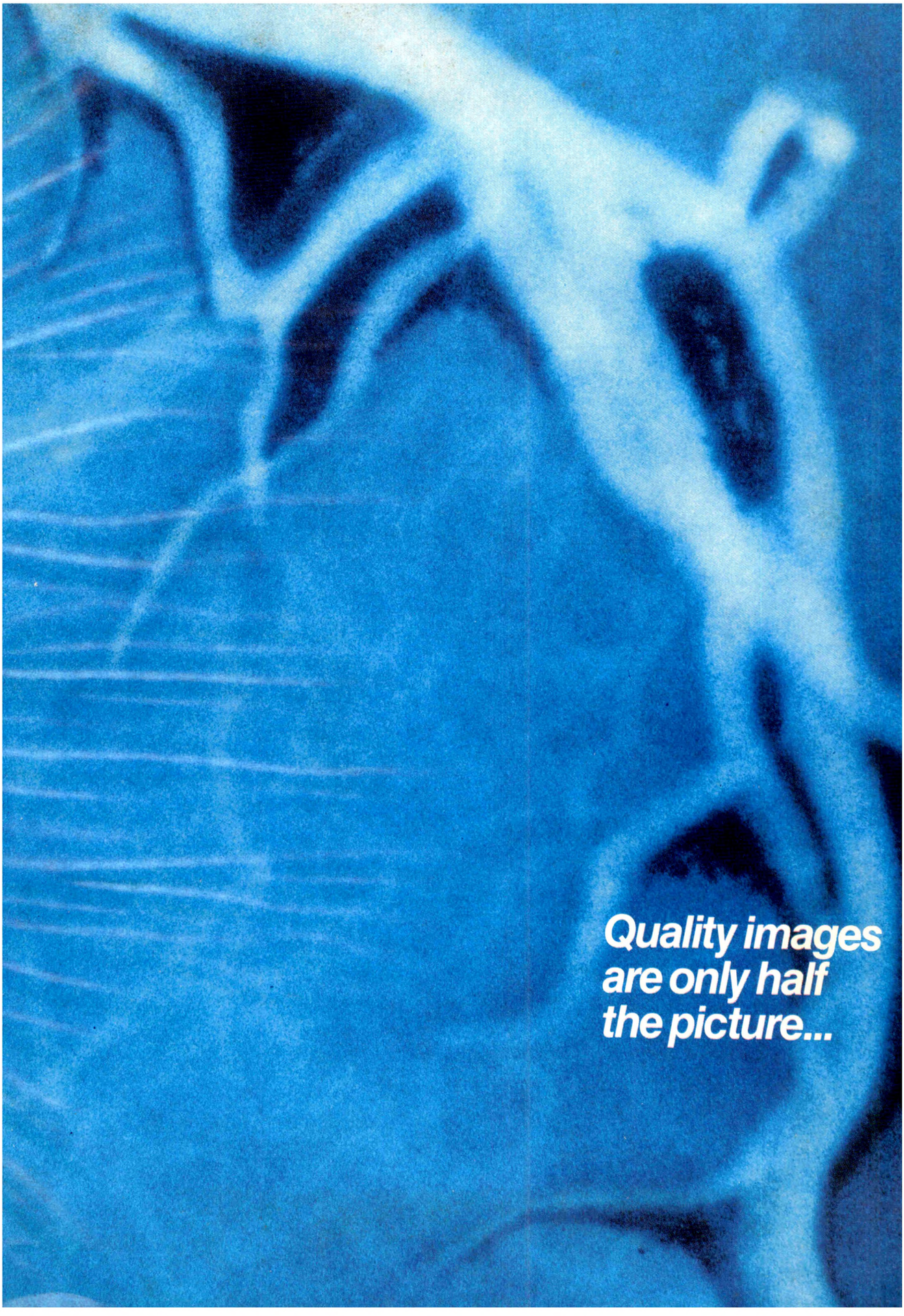
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WARNINGS

Serious or fatal reactions have been associated with the administration of iodine containing radiopaque media. It is of utmost importance to be completely prepared to treat any contrast medium reaction.

As with any contrast medium, serious neurologic sequelae, including permanent paralysis, can occur following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord. The injection of a contrast medium should never be made following the administration of vasopressors, since they strongly potentiate neurologic effects.

In patients with subarachnoid hemorrhage, a rare association between contrast administration and clinical deterioration, including convulsions and death, has been reported. Therefore, administration of intravascular iodinated contrast media in these patients should be undertaken with caution.

A definite risk exists in the use of intravascular contrast agents in patients who are known to have multiple myeloma. In such instances anuria has developed, resulting in progressive uremia, renal failure and eventually death. Although neither the contrast agent nor dehydration has separately proved to be the cause of anuria in myeloma, it has been speculated that the combination of both may be a causative factor. The risk in myelomatous patients is not a contraindication to the procedure; however, partial dehydration in the preparation of these patients for the examination is not recommended since this may predispose to precipitation of myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over 40, should be considered before instituting intravascular administration of contrast agents.

Administration of radiopaque materials to patients known or suspected to have pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for treatment of a hypertensive crisis should be available.

Since intravascular administration of contrast media may promote sickling in individuals who are homozygous for sickle cell disease, fluid restriction is not advised.

In patients with advanced renal disease, iodinated contrast media should be used with caution and only when the need for the examination dictates, since excretion of the medium may be impaired. Patients with combined renal and hepatic disease, those with severe hypertension or congestive heart failure and recent renal transplant recipients present an additional risk.

Renal failure has been reported in patients with liver dysfunction who were given an oral cholecystographic agent followed by an intravascular iodinated radiopaque agent and also in patients with occult renal disease, notably diabetics and hypertensives. In these classes of patients there should be no fluid restriction and every attempt made to maintain normal hydration prior to contrast medium injection, since dehydration is the single most important factor influencing further renal impairment.

Caution should be exercised in performing contrast medium studies in patients with endotoxemia and/or those with elevated body temperatures.

Reports of thyroid storm occurring following the intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, suggest that this additional risk be evaluated before use of this drug. Iodine-containing contrast agents may alter the results of thyroid function tests which depend on iodine estimation, e.g., PBI, and may also affect results of radioactive iodine uptake studies. Such tests, if indicated, should be performed prior to the administration of this preparation.

PRECAUTIONS

Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. All procedures utilizing contrast media carry a definite risk of producing adverse reactions. While most reactions are minor, life-threatening and fatal reactions may occur without warning, and this risk must be weighed against the benefit of the procedure. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. If a serious reaction should occur, immediately discontinue administration. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration. (See ADVERSE REACTIONS.)

Preparatory dehydration is dangerous and may contribute to acute renal failure in infants, young children, the elderly, patients with pre-existing renal insufficiency, patients with multiple myeloma, patients with advanced vascular disease and diabetic patients.

Acute renal failure has been reported in diabetic patients with diabetic nephropathy and in susceptible non-diabetic patients (often elderly with pre-existing renal disease) following the administration of iodinated contrast agents. Therefore, careful consideration of the potential risks should be given before performing this radiographic procedure in these patients.

Severe reactions to contrast media often resemble allergic responses. This has prompted the use of several provocative pretesting methods, none of which can be relied on to predict severe reactions. No conclusive relationship between severe reactions and antigen-antibody reactions or other manifestations of allergy has been established. The possibility of an idiosyncratic reaction in patients who have previously received a contrast medium without ill effect should always be considered. Prior to the injection of any contrast medium, the patient should be questioned to obtain a medical history with emphasis on allergy and hypersensitivity. A positive history of bronchial asthma or allergy (including food), a family history of allergy, or a previous reaction or hypersensitivity to a contrast agent may imply a greater than usual risk. Such a history may be more accurate than pre-testing in predicting the potential for reaction, although not necessarily the severity or type of reaction in the individual case. A positive history of this type does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but does call for caution. (See ADVERSE REACTIONS.)

Prophylactic therapy including corticosteroids and antihistamines should be considered for patients who present with a strong allergic history, a previous reaction to a contrast medium, or a positive pre-test since in these patients the incidence of reaction is two to three times that of the general population. Adequate doses of corticosteroids should be started early enough prior to contrast medium injection to be effective and should continue through the time of injection and for 24 hours after injection. Antihistamines should be administered within 30 minutes of the contrast medium injection. Recent reports indicate that such pre-treatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity. A separate syringe should be used for these injections.

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia which can prolong the circulation time and increase the duration of contact of the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

PRECAUTIONS FOR SPECIFIC PROCEDURES

Pediatric Angiocardiography: It is advisable to monitor for ECG and vital signs changes throughout the procedure.

When large individual doses are administered, sufficient time should be allowed for any observed changes to return to or near baseline prior to making the next injection.

Caution should be used when making right heart injections in patients with pulmonary hypertension or incipient heart failure, since this may lead to increased right side pressures with subsequent bradycardia and systemic hypotension. Patients with pulmonary disease present additional risks.

Caution is advised in cyanotic infants since apnea, bradycardia, other arrhythmias and a tendency to acidosis are more likely to occur.

Since infants are more likely to respond with convulsions than are adults, the amount of total dosage is of particular importance. Repeated injections are hazardous in infants weighing less than 7 kg, particularly when these infants have pre-existing compromised right heart function or obliterated pulmonary vascular beds.

Selective Coronary Arteriography with or without left ventriculography: During the administration of large doses of HEXABRIX, continuous monitoring of vital signs is desirable. Caution is advised in the administration of large volumes to patients with incipient heart failure because of the possibility of aggravating the pre-existing condition. Hypotension should be corrected promptly since it may result in serious arrhythmias.

Special care regarding dosage should be observed in patients with right ventricular failure, pulmonary hypertension, or stenotic pulmonary vascular beds because of hemodynamic changes which may occur after injection into the right heart outflow tract.

Peripheral Arteriography: Moderate decreases in blood pressure occur frequently with intra-arterial (brachial) injections. This change is usually transient and requires no treatment; however, the blood pressure should be monitored for approximately ten minutes following injection.

Extreme caution during injection of the contrast agent is necessary to avoid extravasation and fluoroscopy is recommended. This is especially important in patients with severe arterial disease.

Cerebral Angiography: Cerebral angiography should be performed with special caution in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis or embolism, and migraine.

Intra-Arterial Digital Subtraction Angiography: The risks associated with IA-DSA are those usually attendant with catheter procedures. Following the procedure, gentle pressure hemostasis is required, followed by observation and immobilization of the limb for several hours to prevent hemorrhage from the site of arterial puncture.

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

Intravenous Digital Subtraction Angiography: The risks associated with IV-DSA include those usually attendant with catheter procedures and include intramural injections, vessel dissection and tissue extravasation. The potential risk is reduced when small test injections of contrast medium are made under fluoroscopic observation to insure that the catheter tip is properly positioned and, in the case of peripheral placement, that the vein is of adequate size.

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

Peripheral Venography: Special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system.

Extreme caution during injection of contrast media is necessary to avoid extravasation and fluoroscopy is recommended. This is especially important in patients with severe arterial or venous disease.

Excretory Urography: Infants and small children should not have any fluid restrictions prior to excretory urography. (See WARNINGS and PRECAUTIONS concerning preparatory dehydration.)

Contrast Enhancement in Body Computed Tomography: Patient cooperation is essential since patient motion, including respiration, can markedly affect image quality. The use of an intravascular contrast medium can obscure tumors in patients undergoing CT evaluation of the liver, resulting in a false negative diagnosis. Dynamic CT scanning is the procedure of choice for malignant tumor enhancement.

Arthrography: Strict aseptic technique is required to prevent the introduction of infection. Fluoroscopic control should be used to insure proper introduction of the needle into the synovial space and prevent extracapsular injection. Aspiration of excessive synovial fluid will reduce the pain on injection and prevent the dilution of the contrast agent. It is important that undue pressure not be exerted during the injection.

Hysterosalpingography: Caution should be exercised in patients suspected of having cervical or tubal carcinoma to avoid possible spread of the lesion by the procedure. Delayed onset of pain and fever (1-2 days) may be indicative of pelvic infection.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to evaluate carcinogenic potential. However, animal studies suggest that this drug is not mutagenic and does not affect fertility in males or females.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to two times the maximum adult human dose and have revealed no evidence of impaired fertility or harm to the fetus due to HEXABRIX. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Ioxaglate salts are excreted unchanged in human milk. Because of the potential for adverse effects in nursing infants, bottle feedings should be substituted for breast feedings for 24 hours following the administration of this drug.

Pediatric Use: Safety and effectiveness in children has been established in pediatric angiocardiography and intravenous excretory urography. Data have not been submitted to support the safety and effectiveness of HEXABRIX in any other indication.

(Precautions for specific procedures receive comment under that procedure.)

ADVERSE REACTIONS

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physiochemical properties of the contrast media, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

NOTE: Not all of the following adverse reactions have been reported with HEXABRIX. Because HEXABRIX is an iodinated intravascular contrast agent, all of the side effects and toxicity associated with agents of this class are theoretically possible, and this should be borne in mind when HEXABRIX is administered.

Severe, life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred following the administration of HEXABRIX as well as other iodine-containing contrast agents. Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature, reported deaths from the administration of conventional iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent).

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, or myocardial ischemia or infarction may occur during coronary arteriography and left ventriculography.

The most frequent adverse reactions are nausea, vomiting, facial flush and a feeling of body warmth. These are usually of brief duration. In double-blind clinical trials, HEXABRIX produced less discomfort upon injection (pain and heat) when compared to various other contrast agents. Other reactions include the following:

Hypersensitivity reactions: Dermal manifestations of urticaria with or without pruritus, erythema and maculopapular rash. Dry mouth. Sweating. Conjunctival symptoms. Facial, peripheral and angioneurotic edema. Symptoms related to the respiratory system include sneezing, nasal stuffiness, coughing, choking, dyspnea, chest tightness and wheezing, which may be initial manifestations of more severe and infrequent reactions including asthmatic attack, laryngospasm and bronchospasm with or without edema, pulmonary edema, apnea and cyanosis. Rarely, these allergic-type reactions can progress into anaphylaxis with loss of consciousness, coma, severe cardiovascular disturbances, and death.

Cardiovascular reactions: Generalized vasodilation, flushing and venospasm. Occasionally thrombosis or, rarely, thrombophlebitis. Extremely rare cases of disseminated intravascular coagulation resulting in death have been reported. Severe cardiovascular responses include rare cases of hypotensive shock, coronary insufficiency, cardiac arrhythmia, fibrillation and arrest. These severe reactions are usually reversible with prompt and appropriate management; however, fatalities have occurred.

Technique reactions: Extravasation with burning pain, hematomas, ecchymosis and tissue necrosis, vascular constriction due to injection rate, thrombosis and thrombophlebitis.

Neurological reactions: Spasm, convulsions, aphasia, syncope, paresis, paralysis resulting from spinal cord injury and pathology associated with the syndrome of transverse myelitis, visual field losses which are usually transient but may be permanent, coma and death.

Other reactions: Headache, trembling, shaking, chills without fever, hyperthermia and lightheadedness. Temporary renal shutdown or other nephropathy.

Pediatric angiocardiography has been complicated by intramural injection with marked adverse effects on cardiac function.

During selective coronary arteriography with or without left ventriculography, patients may have clinically insignificant ECG changes. The following adverse effects have occurred in conjunction with the administration of iodinated intravascular contrast agents for this procedure: hypotension, shock, anginal pain, myocardial infarction, cardiac arrhythmias (bradycardia, ventricular tachycardia, ventricular fibrillation) and cardiac arrest. Fatalities have been reported. Complications to the procedure include dissection of coronary arteries, dislodgement of atheromatous plaques, perforation, hemorrhage and thrombosis.

Following peripheral arteriography, hemorrhage and thrombosis have occurred at the puncture site of the percutaneous injection. Brachial plexus injury has been reported following axillary artery injection.

The major causes of cerebral arteriographic adverse reactions appear to be repeated injections of the contrast material, administration of doses higher than those recommended, the presence of occlusive atherosclerotic vascular disease and the method and technique of injection. Adverse reactions are normally mild and transient. A feeling of warmth in the face and neck is frequently experienced. Infrequently, a more severe burning discomfort is observed. Transient visual hallucinations have been reported. Serious neurological reactions that have been associated with cerebral angiography and not listed under Adverse Reactions include stroke, amnesia and respiratory difficulties. Visual field defects with anopsia and reversible neurological deficit lasting from 24 hours to 48 hours have been reported. Confusion, disorientation with hallucination, and absence of vision sometimes lasting for one week have also been reported. Cardiovascular reactions that may occur with some frequency are bradycardia and either an increase or decrease in systemic blood pressure. The blood pressure change is transient and usually requires no treatment. Arthrography may induce joint pain or discomfort which is usually mild and transient but occasionally may be severe and persist for 24 to 48 hours following the procedure. Effusion requiring aspiration may occur in patients with rheumatoid arthritis. Fever and pain, cramping and tenderness of the abdomen have been reported following hysterosalpingography.

OVERDOSAGE

Overdosages may occur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms may include cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma and cardiac arrest. Treatment of an overdose is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

Ioxaglate salts are dialyzable.

The intravenous LD_{50} values of HEXABRIX (in grams of iodine/kilogram body weight) were 11.2 g/kg in mice, >8 g/kg in rats, >6.4 g/kg in rabbits and >10.2 g/kg in dogs.

DOSAGE AND ADMINISTRATION

Details on dosage are provided in the package insert. *CONSULT FULL PACKAGE INSERT BEFORE USE.*

Rev. Jan. 1987

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Validation of Double-Spike Electrograms as Markers of Conduction Delay or Block in Atrial Flutter

FRANCISCO G. COSIO, MD, FERNANDO ARRIBAS, MD, JOSE MARIA BARBERO, MD, CARLOS KALLMEYER, MD, and ANTONIO GOICOLEA, MD

Recent mapping studies of atrial flutter have shown that fragmented electrograms can be found in most cases from the posterior, posteroseptal and posterolateral walls of the right atrium. The fragmentation pattern most often consists of a double spike. To further assess double-spike electrograms as a possible marker of conduction delay, bipolar electrograms were continuously recorded during atrial overdrive pacing of common flutter from the right atrium (7 patients) and from the proximal coronary sinus (5). Baseline double-spike separation of 50 to 130 ms was unchanged in 1 patient and slightly increased (5 to 25 ms) in 4 by coronary sinus pacing. The electrogram sequence was unchanged and the surface morphology was similar to that of basal flutter. Right atrial pacing decreased double-spike separation by 25 to 85 ms from basal values of 45 to 175 ms (23 to 83%), suggesting fusion in the area of fragmented electrograms. These findings suggest that double-spike electrograms represent activation on both sides of a conduction delay zone. The changes induced in these electrograms by pacing from the anterior right atrium and the coronary sinus are consistent with flutter circuits rotating counterclockwise (frontal plane) in the posterior right atrial wall in common atrial flutter.

(Am J Cardiol 1988;61:775–780)

The mechanism of atrial flutter has been studied in experimental and naturally occurring animal models.[1–5] Reentry has been the common underlying mechanism, conduction delay or block being essential either as a generator of a fixed obstacle for the activation front[2–4] or by slowing conduction velocity in part or all the circuit.[1,4]

Human flutter is defined largely on an electrocardiographic basis, considering atrial wave cycle length and morphology.[6,7] The changes induced in flutter cycles by overdrive pacing or extrastimuli[8,9] support a reentrant mechanism; however, little information is available on the configuration of the reentrant circuits and the participation of localized conduction delays.

Recent clinical mapping studies,[10–12] including work from our laboratory, suggest that most flutter circuits are contained in the right atrium, have a rather large amplitude and rotate around the inferior vena cava. Abnormal, fragmented electrograms suggesting areas of abnormal conduction have been recorded within the circuit in both human and animal flutter.[5,11–13]

The present study reports the changes induced by overdrive pacing in the fragmentation pattern that help understand the meaning of these abnormal electrograms and shed new light on the mechanisms underlying atrial flutter.

Methods

We reviewed the recordings obtained during atrial pacing in 11 patients with atrial flutter. Two conditions had to be fulfilled by all participants: identification during atrial mapping of a large right atrial circuit and a record of fragmented electrograms inscribing double-spike patterns. Clinical and electrocardiographic data are listed in Table I. All patients had a clinical indication for flutter cardioversion and gave consent for it and the complementary mapping procedure. The

From the Cardiology Service of Hospital Central de la Cruz Roja and the Department of Medicine, Medical School of Universidad Complutense, Madrid, Spain. This study was supported in part by grant 2425/83 from the Comisión Asesora para Investigación Cientifica y Tecnológica (CAICYT) del Ministerio de Educación and by a grant from Medtronic Hispania S.A. (Premio Medtronic de Investigación 1985). Manuscript received August 24, 1987; revised manuscript received December 7, 1987, and accepted December 8.

Address for reprints: Francisco G. Cosio, MD, Jefe de Servicio de Cardiologia, Hospital Central de la Cruz Roja, Avenida Reina Victoria 22, 28003 Madrid, Spain.

TABLE I Summary of Clinical and Electrocardiographic Findings

Pt	Diagnosis	Drug	Flutter Type	Mapping (%)	DS Site	Cycle Length	DS Sep
1	COLD	Digoxin	Common	86	MPLRA	180 BASAL	50
						160 P CS	60
2	Constrictive pericarditis	Digoxin	Common	64	MPRA	205 BASAL	50
						160 P CS	55
						140 P CS	60
3	COLD and HBP	Quinidine	Common	82	MPLRA	300 BASAL	130
						280 P CS	130
						260 P CS	130
4	Mitral stenosis	Digoxin Quinidine	Common	56	LPRA	215 BASAL	50
						185 P CS	65
						165 P CS	75
5	Alcoholic cardiomyopathy	Quinidine	Common	76	LPLRA	210 BASAL	70
						190 P CS	75
						165 P CS	80
						150 P CS	95
						175 P RA	75
						160 P RA	55
						150 P RA	20
6	Steinert's disease	—	Common	84	LPRA	225 BASAL	90
						185 P RA	55
						170 P RA	15
7	Alcoholic cardiomyopathy COLD	Quinidine Amiodarone	Low voltage	96	LSRA	260 BASAL	45
						230 P RA	30
						200 P RA	30
8	WPW	Propafenone	Rare	61	HPRA	285 BASAL	55
						230 P RA	30
						200 P RA	30
9	Restrictive cardiomyopathy	Quinidine	Low voltage	75	LPLRA	300 BASAL	175
						220 P RA	90
10	Pulmonary embolism	Digoxin Quinidine	Common	100	LPRA	265 BASAL	70
						180 P RA	25
11	Sick sinus syndrome	—	Common	88	LSRA	210 BASAL	70
						185 P RA	40

COLD = chronic obstructive lung disease; CS = coronary sinus; DS Sep = double-spike separation; DS Site = location of the double-spike electrograms; HBP = high blood pressure; HPRA = high posterior right atrium; LPLRA = low posterolateral right atrium; LPRA = low posterior right atrium; LSRA = low septal right atrium; Mapping (%) = percent of the flutter cycle covered by the recorded electrograms; MPLRA = midposterolateral right atrium; MPRA = midposterior right atrium; P = paced; RA = right atrium; WPW = Wolff-Parkinson-White syndrome.

study was approved by the Hospital Research Committee.

Quadripolar catheter-electrodes were introduced through a right antecubital vein and 1 or 2 femoral veins under local anesthesia. Bipolar (1-cm separation) electrograms were amplified and filtered (40 to 500 Hz) in Electronics for Medicine amplifiers. Recordings were made at a paper speed of 100 mm/s. Amplifier gain was adjusted to make recorded electrograms 2 to 3 cm in size. Surface orthogonal leads X, Y and Z (Frank) or standard leads I, II and III were used as reference.

Mapping procedure: A quadripolar catheter-electrode was advanced to the coronary sinus, with recordings obtained from the most distal position attainable to the proximal portions, at intervals of 1 to 2 cm. Another quadripolar catheter electrode was advanced to the right atrial appendage and recordings obtained from the distal (appendage) and proximal (right atrial "roof") pairs of electrodes. One or both of these catheters were left in place as fixed endocardial references for the remainder of the recordings obtained sequentially by means of a third or still a fourth catheter-electrode. Electrode position was checked by biplane fluoroscopy. Using the entrance of both venae cavae as references, the right atrial wall was divided into "septal," "posterior," "lateral" and "anterior," with 3 recording levels made in each: "high" (cranial), "mid" and "low" (caudal). In some cases we made detailed recordings around the superior or inferior vena cava entrances, or both.

Maps were constructed on a schematic representation of both atria, as shown in Figure 1. The onset of activation (0 point) was ascribed arbitrarily. The electrograms were timed at the onset of the first sharp deflection. If electrogram duration was increased to ≥50 ms or if there were double or multiple spikes, the electrograms were represented by a double figure, indicating the onset and end.

Pacing procedure: Pacing was from the coronary sinus in 5 patients and from the high or mid anterior right atrium in 7. One patient was paced from both sites. Progressively shorter cycle lengths were used, in 10 to 20 ms runs, until sinus rhythm or atrial fibrillation resulted. Four endocardial recordings were obtained during pacing in 10 patients and 3 in 1 (the area with double-spike electrograms was included in all cases).

For the sake of clarity some of the recordings have been eliminated from the figures shown.

Statistical analysis: Student *t* test for paired data was used to analyze the statistical significance of the observed differences.

Results

Baseline data: Clinical and electrophysiologic features are listed in Table I. Flutter cycle length ranged from 180 to 300 ms. All patients with cycles longer than 250 ms were receiving antiarrhythmic drugs. Flutter wave pattern was "common" in 8, "rare" (positive waves in inferior leads) in 1 and characterized by low-voltage activity in 2. All patients not showing a common flutter pattern were receiving antiarrhythmic drugs.

Flutter maps covered 56 to 100% of the cycle length and were compatible in all cases with large circuits contained in the right atrium. Activation followed a caudocranial direction on the septal right atrium and a craniocaudal direction on the lateral and anterior walls. The circuit was closed by means of a "return" path between the inferior vena cava and the tricuspid valve. Activation of the coronary sinus proceeded from right to left in all cases. A typical map is shown in Figure 1.

Fragmented "double spike" electrograms were recorded from the posterior, posterolateral or posteroseptal wall. Double-spike separation measured between the onset of each spike ranged from 45 to 175 ms. Although the stability of the double-spike electrograms was remarkable for recording periods of up to 20 minutes while the recording position was stable, small displacements of ≤1 cm could change the double-spike to a single-spike electrogram.

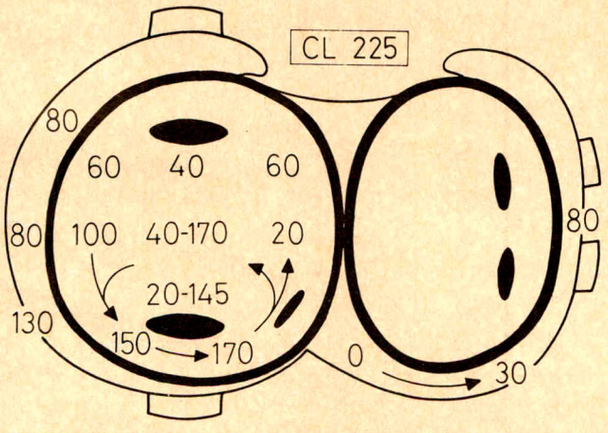

FIGURE 1. Typical flutter map obtained from patient 6. The atria are represented from an "anterior" view, as if the ventricles had been cut off and the atria were seen with a wide-angle lens from the tricuspid and mitral rings. The anterior wall is represented "outside" the tricuspid ring. The openings of the coronary sinus, venae cavae and left pulmonary veins are shown. The onset of activation is arbitrarily assigned. The *arrows* indicate the suggested activation pathway. The double figures indicate areas of fragmented electrograms and mark the onset and end of local electrograms.

Changes in double-spike electrograms during pacing: Complete capture of the atria was shown during pacing by surface and endocardial recordings. Double-spike separation changes followed 2 different patterns related to the pacing site.

Coronary sinus pacing produced no change in 1 patient and a slight increase in 4 (Figure 2). Baseline separation ranged from 50 to 130 ms and the increase recorded in these 4 cases ranged from 5 to 25 ms (6 to 50%). Mean baseline separation of 70 ± 35 ms (standard deviation) increased to 84 ± 30 ms ($p < 0.05$). The increase was related to pacing cycle length (Figure 3).

In 7 cases pacing was in the high or mid anterior right atrium. Baseline separation ranged from 45 to 175 ms (83 ± 43) and during pacing it decreased consistent-

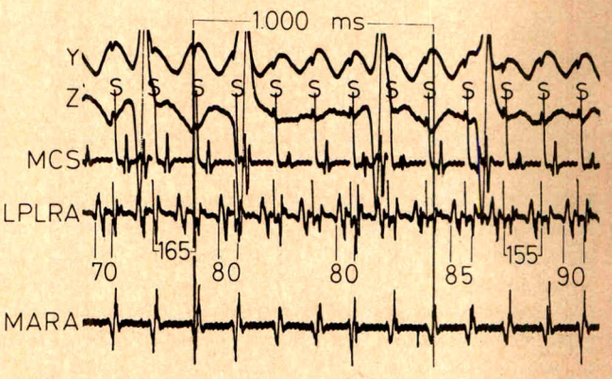

FIGURE 2. Effect of coronary sinus stimulation in patient 5. Surface leads Y and Z (Frank) and endocardial electrograms from midcoronary sinus (MCS), low posterolateral right atrium (LPLRA) and midanterior right atrium (MARA) are shown. Pacing artifacts are best seen at MCS. A double-spike electrogram is recorded at LPLRA. As pacing cycle length decreases from 165 ms (*left*) to 155 ms (*right*), separation between the 2 spikes at LPLRA increases from 70 to 90 ms. Note that flutter waves remain negative in lead Y during overdrive pacing. S = stimulus artifact.

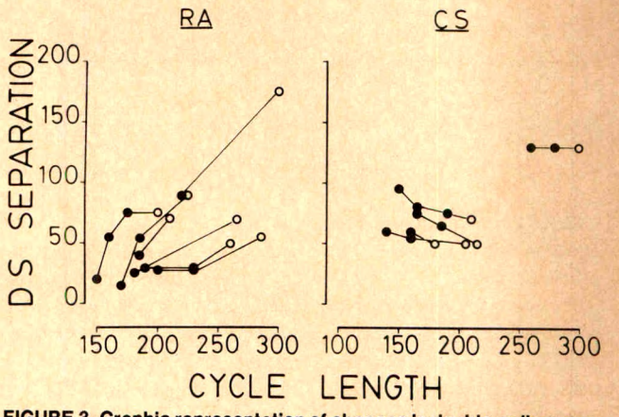

FIGURE 3. Graphic representation of changes in double-spike separation induced by pacing in the anterior right atrium and coronary sinus. All values are in ms. *Open circles* indicate basal flutter values and *solid circles* pacing-induced cycle lengths. CS = coronary sinus pacing; DS = double spike; RA = right atrial pacing.

ly by 15 to 75 ms (23 to 89%) to a mean of 38 ± 25 ($p < 0.01$) (Figure 4). Of 4 cases paced at more than 1 cycle length, 2 showed a progressive fusion of the double spike and 2 showed a decrease in separation with the initial pacing run but without additional decreases with shorter cycle lengths (Figure 3).

The pattern of double-spike capture was also different. Pacing from the coronary sinus captured both components simultaneously, whereas pacing from the right atrium consistently resulted in advancement (capture) of the second component of the double spike one cycle earlier than the first (Figure 4).

Patterns of flutter interruption: In the case of patient 8, a decrease in spike separation from 55 to 30 ms at a pacing cycle length of 230 ms and no further narrowing occurred with a 200 ms cycle; however, a change in electrogram sequence led to flutter interruption at this shorter cycle (Figure 5). Six other patients developed sinus rhythm after complete disorganiza-

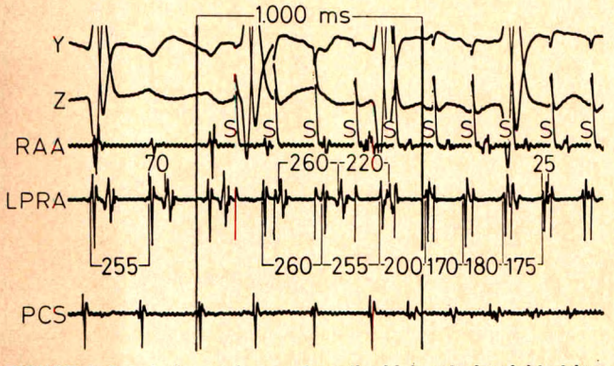

FIGURE 4. Onset of a pacing run from the high anterior right atrium in patient 10. Surface leads Y and Z (Frank) and endocardial electrograms from the right atrial appendage, low posterior right atrium and proximal coronary sinus are shown. Atrial capture occurs with the third pacing stimulus at the right atrial appendage. One cycle later, the second component of the double-spike electrogram of the low posterior right atrium is advanced (indicating capture), while the first component still has not changed sequence. As the paced captured cycle stabilizes at 175 ms, the 2 spikes have almost fused completely into 1. LPRA = low posterior right atrium; PCS = proximal coronary sinus; RAA = right atrial appendage; S = stimulus artifact.

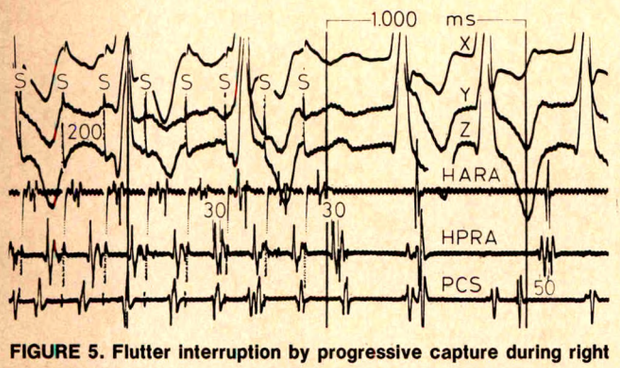

FIGURE 5. Flutter interruption by progressive capture during right atrial pacing in patient 8. Surface leads X, Y and Z (Frank) and endocardial electrograms from high anterior right atrium, high posterior right atrium and proximal coronary sinus are shown. With a pacing cycle length of 200 ms, progressive change in electrogram sequence develops (note the change in temporal relation between the high posterior right atrium and the proximal sinus) and flutter waves become positive in lead Y and Z. When pacing stops, flutter has been substituted by an atrioventricular reentrant tachycardia using a left-sided accessory pathway. Fragmented electrograms are now slightly wider than during pacing. HARA = high anterior right atrium; HPRA = high posterior right atrium; PCS = proximal coronary sinus; S = stimulus artifact.

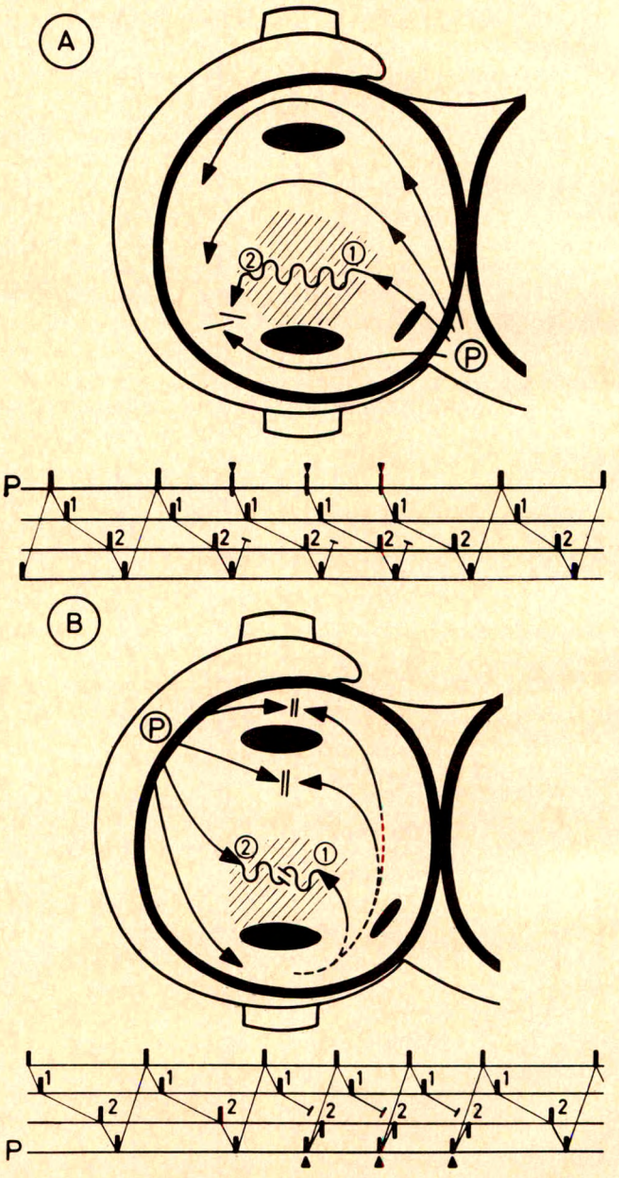

FIGURE 6. *A*, schematic representation of the events proposed during entrainment with orthodromic penetration of the abnormal conduction area. *B*, events proposed during entrainment with antidromic penetration of the abnormal conduction area. Two consecutive activation cycles are shown, the last paced cycle and the preceding entrained cycle. The tail of the before-last cycle has been marked by an interrupted trace. Numbers 1 and 2 mark the postulated origins of the first and second spike of the double electrograms. P = pacing site.

tion of flutter. In 3 this period of disorganization lasted 1 to 5 seconds and in the remaining 3 it was sustained as atrial fibrillation for 30 seconds to 3 hours.

Discussion

Our group of patients was selected in order to study the effect of orthodromic and antidromic penetration of the abnormal electrogram zone. As we knew the direction of flutter activation we could establish that pacing from the coronary sinus entered this area orthodromically, whereas penetration during anterior right atrial pacing was antidromic (Figure 6). Coronary sinus pacing did not change electrogram sequence or flutter wave morphology, the only change observed being a slight widening of double-spike separation probably due to some degree of decremental conduction. This was consistent with the situation described as "concealed entrainment,"[14,15] in which the flutter circuit is entrained but fusion cannot be demonstrated (Figure 6A). Fusion would probably be demonstrated if recordings were obtained from the area between the inferior vena cava and the tricuspid ring.

Pacing from the anterior right atrium consistently narrowed double-spike separation, with the particular feature of advancing the second spike 1 cycle before the first. This most likely represents antidromic penetration of the abnormal electrogram area and fusion in its midst with the orthodromic activation front (Figure 6B). Such reproducible behavior rules out the possibility of the double-spike electrograms being due to motion artifacts. Bipolar recordings would seem to be picking up 2 activation fronts, close anatomically but widely separated in time.

This situation may be due to an area of slow conduction separating 2 fast conduction zones, in this case the 2 spikes representing entrance and exit of the activation front in the slow conduction area (Figure 7) as proposed by Brachman et al[16] in ventricular reentrant circuits. This interpretation also is supported by the work of Gardner et al[17] in infarcted ventricular myocardium showing that fragmented, double- or multiple-spike electrograms are inscribed as an activation front crosses an area where normal myocardial fibers are separated by areas of necrosis. Another possibility is that a "line" of complete block may be present as in 1 of the canine flutter models of Boineau et al.[4] Our mapping technique was too crude to allow us to separate these 2 possibilities, and, although we can propose that conduction delays in the posterior right atrium seem to underlie most atrial flutter circuits in men, we cannot say if conduction through this area constitutes part of the circuit or if the area acts only as a barrier, "enlarging" the central anatomic obstacle made by the inferior vena cava. On the other hand, we have not ruled out the presence of more areas of slow conduction in other parts of the circuit that seem to constitute an obligatory "return" pathway, particularly in the caudal parts of the right atrium that are anatomically more complex and technically more difficult to map, as is the area around the inferior vena cava, coronary sinus and tricuspid valve. Klein et al[18] described slow conduction in this area in 2 cases of atrial flutter undergoing epicardial mapping in the operating room.

Anisotropic conduction[19] could play a role in these conduction delays because the activation front seemed to course perpendicularly to the middle and posterior internodal pathways in the posterior atrial wall. Conduction across parallel bundles of myocardial fibers can be quite slow and inscribe fragmented local electrograms.[20]

Another important question is the possible participation of these conduction abnormalities in the flutter circuit. The observations during flutter interruption in patient 8 are suggestive in this respect. Maximal reduction in fragmentation width occurred in this patient at a pacing cycle length of 230 ms, but it was necessary to reduce cycle length to 200 ms to penetrate the circuit deeply enough to change the overall electrogram sequence, and this led to flutter interruption. If this means inversion of conduction through the double-spike zone, then conduction would appear to be slower in the orthodromic than in the antidromic sense. Indeed, when flutter was substituted by a reentrant atrioventricular tachycardia using a left anomalous pathway, activation entered this area in the same direction as the flutter circuit and the local electrogram was wider than during pacing from the anterior right atrium at a much shorter cycle length. Unfortunately, all the other patients developing sinus rhythm went through periods of disorganization and we could not reproduce this observation.

Future studies should try to establish whether the block or slow conduction are unidirectional and if a critical degree of delay in this area during its orthodromic penetration by coronary sinus pacing is a sufficient and necessary condition for atrial flutter induction.

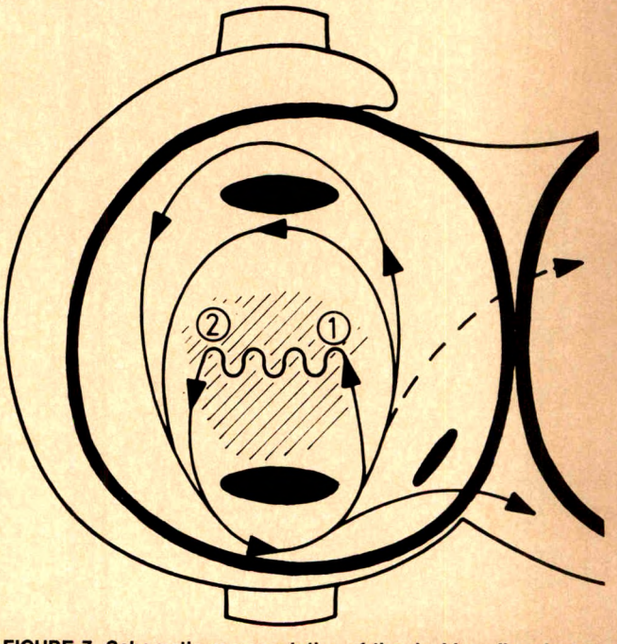

FIGURE 7. Schematic representation of the double-spike electrogram area conceived as a slow-conduction zone supporting the flutter circuit. The numbers indicate the suggested origin of the first and second spike of the electrograms.

Acknowledgment: We appreciate the technical assistance of Guadalupe López, DE, Pilar Gómez, DE, Teresa Soria, DE, Anabel Tardio, DE, and Teresa Jiménez, DE.

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Characteristics of Entrainment During Autodecremental Atrial and Ventricular Stimulation

AGUSTIN CASTELLANOS, MD, LIAQAT ZAMAN, MD, PEDRO FERNANDEZ, MD, BOLIVAR PORTILLO, MD, BAROUH V. BERKOVITS, EE, and ROBERT J. MYERBURG, MD

The entrainment characteristics of orthodromic circus movement tachycardias occurring during autodecremental atrial and ventricular stimulation were studied in 9 patients with manifest Wolff-Parkinson-White syndrome. The phenomenon occurred in 34 of 38 episodes of tachycardia during autodecremental atrial stimulation. It was not seen in 4 episodes because the first impulse penetrating the circuit terminated the arrhythmia. Invariably, the HH and VV intervals were not equal to, but longer than, the stimulus-stimulus intervals, thus not fulfilling the definition of "classic" (constant cycle length) entrainment postulated by Okumura et al. Furthermore, the first 2 of the 3 diagnostic criteria were not demonstrated and the third only could be demonstrated in 7 episodes. Tachycardia termination was achieved in all 38 episodes. Entrainment occurred during autodecremental ventricular stimulation in 79 of 80 episodes, with the AA and $H^{-}H^{-}$ intervals (when visible) being equal to the corresponding paced cycle lengths. Moreover, the intervals between the last paced ventricular beat and the first ventricular beat of the resumed tachycardia were invariably longer than the last stimulus-stimulus intervals. These characteristics were those which Okumura et al attributed to "concealed" entrainment. Tachycardia termination was achieved in 77 of 80 episodes.

In summary: (1) autodecremental atrial pacing produced a specific form of entrainment that did not fulfill the "classic" definition of Okumura et al; (2) autodecremental ventricular pacing consistently produced "concealed" entrainment; and (3) autodecremental stimulation was very effective in terminating 115 of 118 (98%) of episodes of circus movement tachycardias.

(Am J Cardiol 1988;61:781–786)

In 1983, Waldo et al[1] showed that entrainment of circus movement tachycardias during overdrive pacing constituted an excellent model for the understanding of a variety of electrophysiologic phenomena occurring in patients with reentrant circuits. Most studies[1–4] dealing with overdive pacing of circus movement tachycardias have been performed using constant cycle lengths during each pacing run. Therefore, it seemed of interest to discuss the characteristics of the entrainment observed with the recently introduced self-adapting autodecremental mode of stimulation, in which the pacing cycle lengths decrease during each pacing run.[4,6]

From the Division of Cardiology, Department of Medicine, University of Miami School of Medicine, Miami, Florida. Dr. Fernandez is a recipient of training grant HL 07436 from the National Institutes of Health, Bethesda, Maryland. Manuscript received July 31, 1987; revised manuscript received and accepted November 23, 1987.

Address for reprints: Agustin Castellanos, MD, Division of Cardiology (D-39), University of Miami School of Medicine, P.O. Box 016960, Miami, Florida 33101.

Methods

Patients: Nine patients with manifest Wolff-Parkinson-White syndrome and orthodromic circus movement tachycardia of the usual (short RP interval) type constitute the basis of this report. Pertinent information is listed in Table I.

Electrophysiologic studies: These were performed in accordance with previously described criteria,[4,5,7] after explaining the procedure and obtaining informed consent. Briefly, the technique consisted of introducing tetrapolar catheter electrodes to pace, record, or both, from several atrial (A) sites, the His (H) bundle and right ventricle (V). At least 3 surface leads were obtained simultaneously with the intracardiac leads using Electronics for Medicine or Gould ES 1000 recorders.

TABLE I Clinical Data

Pt	Age (yr), Sex	Organic Heart Disease	Location of Accessory Pathway	Tachycardia Cycle Length (ms)	Drug
1	55, F	0	LFW	315–320	0
				265–275	I
2	58, M	0	LFW	370–390	0
3	46, M	0	RFW	360	0
				345–355	FL
4	48, M	0	RFW	390–395	A
5	62, M	DC	RFW	345–355	0
6	19, F	0	AS	290–310	0
7	54, F	0	AS	280–350	0
8	37, M	0	AS	250–260	0
9	61, M	0	PS	310	0

A = amiodarone; AS = anteroseptal; DC = dilated cardiomyopathy; FL = flecainide; I = isoproterenol; LFW = left free wall; PS = posteroseptal; RFW = right free wall.

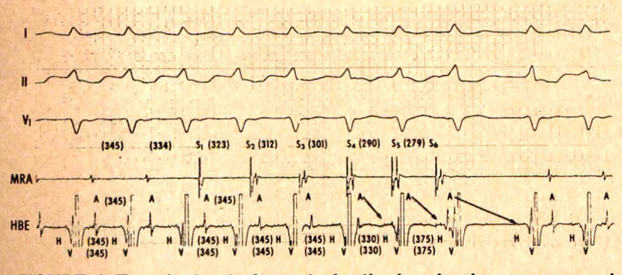

FIGURE 1. Transient entrainment of orthodromic circus movement tachycardia during autodecremental high right atrial stimulation in a patient with a right free wall accessory pathway. Note that during entrainment (oblique arrows from A to H), the HH and VV intervals were not equal to, but longer than, the corresponding stimulus-stimulus (S) intervals. A = atrial electrograms; H = His bundle; HBE = His bundle electrographic lead; MRA = mid-right atrium; V = onset of ventricular electrograms. All intervals are expressed in milliseconds.

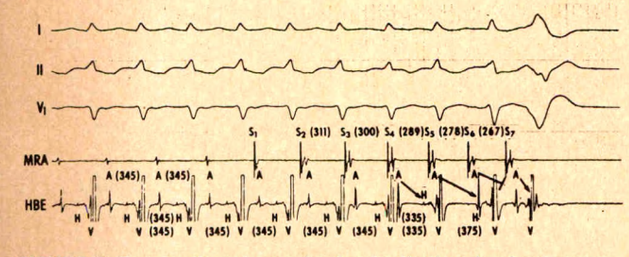

FIGURE 2. Termination of an episode of orthodromic circus movement tachycardia with autodecremental high right atrial stimulation. Presumably, S_6 was blocked in the normal pathway (atrioventricular node) and, as a result, the following impulse which the pacemaker was committed to deliver (because this was the pacing run where it had to emit 7 stimuli) could penetrate the accessory pathway when this structure was no longer refractory. Therefore, S_7 reached the ventricles with a conduction time shorter than that of previous atrial impulses.

At the time of the procedure, 6 patients were not taking any cardioactive medication and 1 was receiving amiodarone. One patient was studied before and after flecainide and 1 before and after a drip infusion of isoproterenol (4 μg/min), given in an attempt to induce this patient's other clinical arrhythmia (atrial fibrillation). The electrophysiologic location of the accessory pathways in every patient is listed in Table I.

Autodecremental pacing: Following completion of the conventional part of the study, the terminals of a ventricular—and subsequently of an atrial—catheter electrode were attached to a specially constructed, self-adapting autodecremental pacemaker (Medtronic) to treat reinduced or spontaneously occurring episodes of circus movement tachycardia.[5] When an activator magnet was placed over the device, it recognized the tachycardia from the intracardiac electrogram and started to emit stimuli.[5] With the program used, each consecutive stimulus (including the first) appeared at intervals 3 to 6% shorter than the cycle length of the tachycardia. Moreover, the initial autodecremental pacing run invariably consisted of 5 stimuli. If the tachycardia was not terminated with this run, the pacemaker delivered 10 beats later 1 additional stimulus in each subsequent run until the arrhythmia was abolished or 14 stimuli emitted. The cycle lengths of the tachycardias ranged between 250 and 395 ms (Table I).

Entrainment (mechanism): During entrainment of a circus movement tachycardia, regardless of the duration (constant or not) of paced cycle lengths, every stimulated impulse penetrates the anterograde limb of the reentry circuit (during atrial pacing) or the retrograde limb (during ventricular pacing) and also collides with the previous retrograde wavefront during atrial pacing or anterograde wavefront during ventricular pacing. Moreover, this occurs in such a way that the tachycardia's potential to resume upon the cessation of pacing is maintained.[1–4,8–11]

Entrainment (definition): Because intervals between electrograms recorded from sites that are essential components of the reentry circuit are equal to the stimulus-stimulus intervals, Okumura et al[2] defined transient "classic" (constant cycle length) entrainment of a tachycardia during rapid stimulation as "an increase in the tachycardia rate to the faster pacing rate." However, as will be demonstrated subsequently, entrainment is best defined during autodecremental pacing as a continuous resetting of the tachycardia circuit.[10]

Entrainment (diagnostic criteria and types): Okumura et al[2] postulated 3 criteria for the diagnosis of "classic" entrainment while pacing the atria: (1) constant fusion except for the last captured beat, which is entrained but not fused; (2) progressive fusion; and (3) localized conduction block to a site(s) for 1 paced beat associated with termination of the tachycardia, followed by activation of that site(s) by the next paced beat from a different direction and with a shorter conduction time. On the other hand, these investigators considered that, during ventricular pacing at constant

cycle lengths, the entrainment was "concealed" if the phenomenon was conceptually present but none of the previous 3 criteria could be demonstrated.

Results

Entrainment during autodecremental atrial pacing: Characteristically, the total number of stimuli in each pacing run did not define how many impulses penetrated the circuit. Thus, in Figure 1 (obtained from a patient with a right free wall accessory pathway), neither S_1, S_2 nor S_3 entered the circuit because the simultaneously occurring HH and VV intervals equalled the tachycardia cycle length (345 ms). Entrainment began when the anterograde atrial impulse produced by S_4 captured the ventricles through the His bundle and thus shortened the corresponding intervals to 330 ms. This impulse also collided, presumably within the accessory pathway, with the retrograde impulse, which, following the simultaneously occurring QRS complex, had penetrated the accessory pathway in a ventricular-auricular direction. The same sequence of events took place after S_5 and S_6. In addition, the ventricular impulse resulting from the QRS complex induced by S_6 (indicated by the longest oblique arrow) penetrated the accessory pathway retrogradely and found no anterograde impulse with which to collide (because atrial pacing had been stopped), and thus was able to reenter the atrioventricular node to resume the tachycardia. During entrainment, the intervals between all recorded atrial electrograms equalled but the HH and VV intervals exceeded the stimulus-stimulus interval (Figure 1). Moreover, there was a gradual increase in the AH intervals. Entrainment was mechanistically present since there was penetration of the anterograde limb and collision, in some part of the circuit, with the preceding retrograde impulse. Indeed, the tachycardia circuit was continually reset.

The *maximal* number of entrained beats in 38 episodes in response to autodecremental atrial stimulation were: 1 in 2 episodes; 2 in 26; 3 in 4 and 4 in 2 (Table II). Entrainment could not be demonstrated in 4 episodes because the first beat penetrating the circuit terminated the arrhythmia.

Okumura's criteria number 1 and 2 for the diagnosis of "classic" entrainment were not met because atrial fusion leading to pure paced atrial beats almost invariably occurred in every pacing run. Furthermore, because entrainment was always seen during a Wenckebach sequence, the last ventricular complex produced by a paced atrial beat appeared at a VV interval which exceeded the corresponding stimulus-stimulus interval (Figure 1).

However, criterion number 3 was observed in 7 episodes (Figure 2). For example, in this figure, S_6 seems to have been blocked at the atrioventricular node, thus terminating the tachycardia. Thereafter, the anterograde impulse produced by S_7 (which had to be emitted because this was the pacing run in which the pacemaker was committed to deliver 7 stimuli) must have reached the accessory pathway when this struc-

TABLE II Results of Autodecremental Atrial Pacing

No. of Episodes	Maximal No. of Paced Beats Producing Entrainment	Minimal No. of Paced Beats Producing Tachycardia Termination
4	*	1
2	1	2
26	2	3
4	3	4
2	4	5

* Entrainment did not occur in 4 episodes.

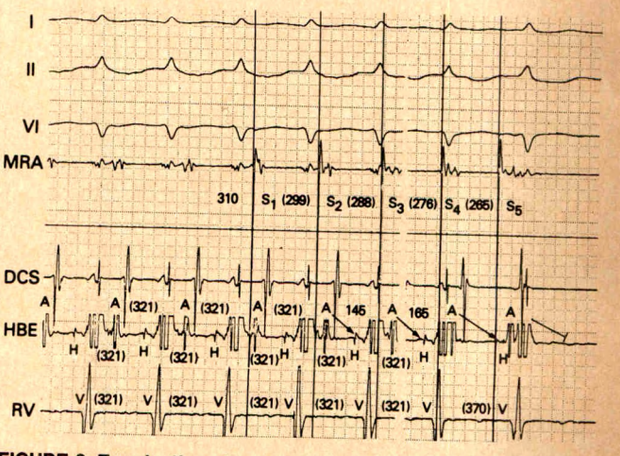

FIGURE 3. Termination of an episode of orthodromic circus movement tachycardia with autodecremental high right atrial stimulation. Note that S_5 was blocked at the atrioventricular node (thus ending the arrhythmia) after S_4 reached the ventricles with a long delay in the normal pathway. DCS = distal coronary sinus; RV = right ventricle.

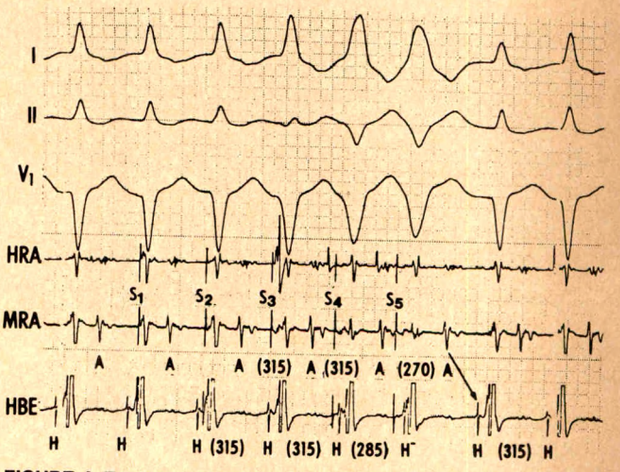

FIGURE 4. Transient entrainment of orthodromic circus movement tachycardia during autodecremental ventricular stimulation in a patient with a left free wall accessory pathway. Although 5 stimuli were emitted, only 1 (S_5) penetrated the reentry circuit, thus shortening the AA interval from 315 to 285 ms. H- indicates what could have been a retrograde His bundle deflection.

TABLE III Results of Autodecremental Ventricular Pacing

No. of Episodes	Maximal No. of Paced Beats Producing Entrainment	Minimal No. of Paced Beats Producing Tachycardia Termination
1	*	1
3	1	2
20	2	3
13	3	4
22	4	5
12	5	6
6	6	7
3	10	†

* Entrainment did not occur in 1 episode; † tachycardia could not be terminated in 3 episodes.

ture was no longer refractory from the concealed retrograde conduction into the accessory pathway produced by the next-to-last (narrow) QRS complex. Thus, S_7 was conducted to the ventricles through a different atrioventricular limb (the accessory pathway) than S_6, but with a much shorter conduction time and a wider (preexcited) QRS complex. Consequently, there was a "localized conduction block to sites (atrioventricular node and ventricles) for 1 paced beat associated with termination of the tachycardia followed by activation of those sites by the next paced beat from a different direction (corresponding to the location of the accessory pathway) and with a shorter conduction time."[2]

Tachycardia termination during autodecremental atrial pacing: Tachycardia termination occurred in all 38 episodes treated with autodecremental atrial stimulation when an impulse was blocked at the atrioventricular node and followed by no additional impulse (Figure 3) or followed by 1 more impulse than the pacemaker (because of programming) was committed to deliver (Figure 2). The former was the termination mode in 31 episodes and the latter in 7 episodes. The *minimal* number of paced beats penetrating the circuit required for termination of the tachycardia is shown in Table II.

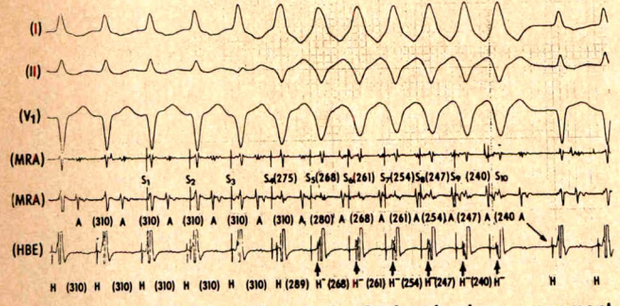

FIGURE 5. Transient entrainment of orthodromic circus movement tachycardia. The characteristics of the phenomenon under consideration were those attributed by Okumura et al[2] to "concealed" entrainment. (See text.)

Entrainment during autodecremental ventricular stimulation: Entrainment (continuous resetting of the tachycardia circuit) was observed in 79 of 80 episodes. The *maximal* number of entrained beats occurring in each episode is presented in Table III (it failed to occur once because the first impulse penetrating the circuit terminated the tachycardia). Again, the total number of stimuli did not define the actual number of impulses entering the circuit. For example, in Figure 4, obtained from a patient with a left free wall accessory pathway, S_1, S_2, S_3 and S_4 failed to penetrate the circuit as determined by the fact that the simultaneously occurring AA and HH intervals equalled the tachycardia cycle length (315 ms). On the other hand, S_5 preexcited the atria through the accessory pathway and thus decreased the AA interval to 270 ms. This impulse (S_5) also penetrated the His bundle retrogradely (as determined by an HH^- interval of 285 ms), reached the atrioventricular node and finally collided in the latter structure with a preceding anterograde atrial impulse.[2,9] Because pacing was stopped after S_5, the atrial impulse produced by this last paced impulse was able to penetrate anterogradely the atrioventricular node and, because there was no retrograde impulse with which to collide (as well as no effective AV nodal refractoriness), it reached the ventricles. Hence, the tachycardia resumed.[2,9]

In Figure 5, obtained from the same patient 5 pacing runs later, only 6 beats penetrated the circuit, although a total of 10 stimuli were delivered. Although transient entrainment was present (from S_5 to S_{10}), the ventricular impulses activated the atria retrogradely via the accessory pathway with a constant (short) ventriculoauricular conduction time and reached, also retrogradely, the atrioventricular node, colliding there with the oncoming anterograde atrial impulses. Consequently, the AA intervals (and the H^-H^- intervals when visible) equalled the stimulus-stimulus intervals.[2,9]

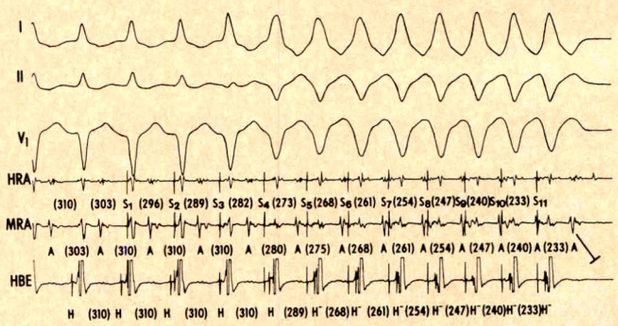

FIGURE 6. Termination of the same episode of orthodromic circus movement tachycardia shown in Figures 4 and 5 with autodecremental ventricular stimulation. Note that the tachycardia ended when, upon cessation of pacing, the atrial impulse produced by the last stimulated beat was unable to traverse the atrioventricular node anterogradely because this structure had been rendered effectively refractory by the preceding anterograde atrial or retrograde ventricular impulses, or both.

Again, as in Figure 4, the atrial impulse produced by the last stimulated beat penetrated the atrioventricular node and, finding no retrograde impulse with which to collide (because pacing had been stopped), traversed this structure to resume the tachycardia. Because the atrioventricular node had been rendered relatively refractory by the last anterograde atrial and (or) retrograde ventricular impulses that had penetrated it, conduction through the atrioventricular node occurred with an AH interval longer than that of the tachycardia. For this reason, the interval between the last paced ventricular beat and the first ventricular beat of the resumed tachycardia was longer than the last stimulus-stimulus interval.

None of the 3 criteria for "classic" entrainment could be demonstrated during autodecremental ventricular pacing. Criteria number 1 and 2 were not present because progressive ventricular fusion leading to pure stimulated beats occurred in each pacing run. Moreover, the interval between the last paced ventricular beat and the first ventricular complex of the resumed tachycardia exceeded the last stimulus-stimulus interval. Criterion number 3 was not seen because either the tachycardia stopped when the last impulse was anterogradely blocked at the atrioventricular node (Figure 6), or, if an additional impulse was emitted, it was conducted retrogradely to the atria via the same (accessory) pathway with the same (short) conduction time. The entrainment, therefore, was considered to have been "concealed."[2]

Tachycardia termination during autodecremental ventricular stimulation: This was achieved in 77 of 80 episodes. The 3 failures occurred in patient 1 during maximal effects of isoproterenol. The *minimal* number of paced beats required to penetrate the circuit and terminate the tachycardia is presented in Table III. Fifty-four episodes terminated, as in Figure 6, with an anterograde block at the atrioventricular node of an impulse reaching the atria retrogradely via the accessory pathway. On the other hand, 23 episodes terminated when a paced ventricular impulse was abruptly blocked retrogradely in the accessory pathway.

Discussion

Entrainment during autodecremental atrial stimulation: Mechanistically, entrainment was indeed present because the electrophysiologic events occurring within the circuit were consistent with the phenomenon under consideration.[1–4,8] Yet, not surprisingly, the definition of Okumura et al[2] for "classic" (constant cycle length) entrainment did not apply because the rate of the tachycardia did not "increase to the faster pacing rate," that is, the HH and VV intervals were not the same, but distinctively longer than the corresponding stimulus-stimulus intervals.[2] Moreover, during autodecremental or constant cycle length, pacing entrainment is *not* best described as an acceleration of the tachycardia rate, for, once paced impulses have penetrated and occupied the reentrant circuit, the original tachycardia impulses are no longer present.[4,5,8,9] For this reaon, defining entrainment as a continuous resetting of the tachycardia circuit seemed more appropriate.[8–10]

Of the 3 diagnostic criteria of Okumura et al,[2] the first 2 could not be demonstrated and the third one only in those episodes were an impulse, presumably blocked at the atrioventricular node, was followed by another (last) impulse which, therefore, reached the ventricle via the accessory pathway (Figure 3).

Entrainment during autodecremental ventricular stimulation: Each time that continuous resetting of the tachycardia circuit occurred, the AA and the H·H· intervals (when detectable) were equal to the stimulus-stimulus intervals. Although this finding was in keeping with Okumura's concept and definition of entrainment ("increase in the rate of the tachycardia to the faster pacing rate"),[2] none of the 3 diagnostic criteria could be demonstrated. Therefore, autodecremental ventricular stimulation, as well as fixed cycle length ventricular pacing, consistently produced "concealed" entrainment.[2]

It should be pointed out that whenever entrainment occurs while pacing the ventricles (autodecrementally or not) and the retrograde impulse penetrates the atrioventricular node slightly after the preceding atrial impulse had entered this structure anterogradely, both impulses presumably collide within the atrioventricular node.[9] If stimulation is performed in such a manner that only 1 additional impulse is delivered in each successive pacing run, the last entrained beat shows an AH interval which increases as the last paced cycle length decreases. Finally, if no retrograde block is present in the accessory pathways at a given pacing run, an anterograde impulse is blocked at the atrioventricular node, entrainment ceases and the tachycardia is terminated.[9] These events take place because the last anterograde atrial impulse is influenced by the aftereffects of the preceding anterograde atrial or retrograde ventricular impulses, or both, which first cause relative refractoriness and finally effective refractoriness. Otherwise, when starting with or using a fixed (longer) number of stimuli, "concealed" entrainment cannot be differentiated from tachycardia termination followed by tachycardia reinitiation.[2,8,9]

Clinical implications: Thirty-eight of 38 episodes and 77 of 80 episodes of tachycardia were terminated with autodecremental atrial and ventricular pacing, respectively. Moreover, the 3 episodes failing with the latter mode responded to the former. The overall success rate (115 of 118 of all episodes, or 98%) indicates that autodecremental pacing is effective in the treatment of tachycardias occurring in patients with manifest Wolff-Parkinson-White syndrome. Because in 3 episodes atrial pacing succeeded when ventricular pacing had failed and because a lesser number of impulses was needed when stimulating from the atria (Tables II and III), it is tempting to conclude that autodecremental atrial stimulation is more "effective" than its ventricular counterpart. However, the number of cases and episodes is too small to reach definite conclusions. Similarly, and in contrast with the study of Charos et al,[6] no comparison was made in the present

work with other (relatively similar) forms of stimulation, such as the constant cycle length overdrive pacing performed by Waldo et al[2] or conventional burst pacing. Hence, no assumptions can be made as to whether autodecremental stimulation is more effective for circus movement tachycardias than those other modes.

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Sensitivity of an Automatic External Defibrillator for Ventricular Tachyarrhythmias in Patients Undergoing Electrophysiologic Studies

MARK D. CARLSON, MD, CHARLES S. FREEMAN, RN, HASAN GARAN, MD, and JEREMY N. RUSKIN, MD

An automatic advisory external defibrillator (AED) was activated during all arrhythmias occurring at the time of 77 electrophysiologic studies in 45 patients. Sustained ventricular tachycardia (VT) occurred during 55 studies in 31 patients and nonsustained VT was induced during 10 studies in 9 patients. Ventricular fibrillation was induced 5 times in 5 patients and atrial arrhythmias with a rapid ventricular response occurred during 7 studies in 4 patients. The AED detection algorithm advised "shock" during 36 of 55 (65%) episodes of sustained VT and all 5 episodes of ventricular fibrillation. The device correctly advised "shock" for all 6 episodes of nonsustained VT that spontaneously terminated after analysis was complete. Thus, the sensitivity of the device for all ventricular arrhythmias analyzed was 47 of 66 (71%). The device recommended "shock" for all 31 episodes of rapid VT and 1 of 2 episodes of atrial fibrillation associated with systemic hypotension (32 of 33, 97%). The 19 episodes of VT for which "no shock" was advised were comparatively slow and were hemodynamically well tolerated. The device recommended "no shock" during all 21 episodes of normal sinus rhythm and all 20 episodes of rapid atrial pacing (cycle length 400 ms) analyzed. "No shock" was advised during 4 episodes of sustained narrow QRS complex supraventricular tachycardia and 4 brief episodes of nonsustained VT that terminated before analysis was complete. Thus, in this study the specificity of the AED for wide complex tachycardias was 100%.

(Am J Cardiol 1988;61:787–790)

Survival and neurologic recovery following out-of-hospital cardiac arrest is improved by decreasing the time between the onset of the event and the initiation of cardiopulmonary resuscitation and defibrillation.[1–9] This has been demonstrated in cities where first responders, including the general public, firefighters and police, perform cardiopulmonary resuscitation and emergency medical technicians rather than paramedics administer electrical defibrillation. Studies in Seattle have demonstrated that survival rates (percent of patients discharged alive) among patients treated by first responders using an automatic external defibrillator (AED) compared favorably to rates among patients treated by emergency medical technicians using a standard external defibrillator.[10,11]

Because time to defibrillation remains the most important predictor of survival following out-of-hospital cardiac arrest, many investigators have suggested an expanded role for the AED.[12] Use of the device by police, corporate personnel, nursing home staff members and family members of patients at high risk for cardiac arrest might further shorten time to defibrillation and improve survival. However, since ventricular tachycardia (VT) often precedes ventricular fibrillation (VF), an AED used in the home or workplace should recognize and convert both ventricular arrhythmias.[13] Previous studies have examined the sensitivity and specificity of the AED for VF alone.[10,13,14] This study examines the sensitivity and specificity of a

From the Clinical Electrophysiology Laboratory and the Department of Medicine, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts. Manuscript received August 12, 1987; revised manuscript received November 20, 1987, and accepted November 22.

Address for reprints: Mark D. Carlson, MD, Cardiac Electrophysiology Laboratory, Massachusetts General Hospital, Boston, Massachusetts 02114.

TABLE I Arrhythmias Induced at Electrophysiology Study

Arrhythmias Induced	Episodes	Pts
Sustained VT	55	31
Nonsustained VT	10	9
Ventricular fibrillation	5	5
Supraventricular tachycardia	7	4
Total	77	45*

* Some patients had more than 1 type of arrhythmia induced on different occasions.
VT = ventricular tachycardia.

TABLE II Advice for Ventricular Tachyarrhythmias

Arrhythmia	Shock	No Shock	Sensitivity (%)
Sustained VT	36	19	65
Nonsustained VT	6	0	100
Ventricular fibrillation	5	0	100
Total	47	19	71

VT = ventricular tachycardia.

commercially available AED for VT in patients undergoing electrophysiologic evaluation for a variety of cardiac arrhythmias.

Methods

Materials: The AED used (Lifepak 200-Physio-Control Corp.) is designed for use outside the hospital by minimally trained personnel. It is small (12.7 × 23.4 × 33.8 cm) and weighs 7 kg. The device has a rechargeable battery and can deliver up to 20 shocks (200 or 360 joules each) during a 3-hour period.

The AED is activated by opening the display module, thereby activating a message screen. Two 12 × 16 cm oval adhesive electrodes are attached to the patient's chest in standard paddle defibrillator positions. These electrodes serve for both monitoring and defibrillation. After electrode attachment the message screen displays "push to analyze." If VT or VF is sensed, "shock advised" appears on the display screen. The user may administer 200 or 360 joules of direct current electricity by pushing a "shock" button. If neither VT nor VF is detected, the message screen displays "no shock advised."

A digital detector determines chest impedance through the electrodes. Static impedance levels determine electrode-to-skin integrity; dynamic impedance detects respiration, chest compressions and body movements. The impedance detector advises that the electrodes are attached to the patient and that there is no chest movement. This reduces the chance of shocking a patient who has spontaneous respirations or is undergoing cardiopulmonary resuscitation at the time of electrocardiogram analysis. Criteria used to recognize VT include: rate above 120 beats/min, QRS complex duration >160 ms and no apparent P waves preceding complexes. QRS morphologhy is examined to determine the likelihood that the rhythm is ventricular or supraventricular in origin. Important distinguishing factors include the amplitude normalized slew rate and the percentage of isoelectric segment in the rhythm. Higher rates increase the probability that the device will recommend "shock." The shock advisory system detection algorithm examines a 2.7-second segment of the electrocardiogram and internally makes a "shock" or "no shock" determination for that segment. A second determination is made on a subsequent 2.7-second segment. If the determinations match, an advisory is displayed. In cases of disagreement, a third segment is analyzed and that determination is displayed. The entire electrocardiogram analysis process requires 6.6 to 11.1 seconds for completion. A relatively motion-free environment is necessary to provide a "noise-free" signal for analysis. Motion can interrupt rhythm analysis for a maximum of 20 seconds before the message screen reverts to the "push to analyze" standby mode.

Protocol: The AED (Physio Control Lifepak 200) was evaluated during 107 consecutive electrophysiologic studies in 66 patients who underwent programmed cardiac stimulation at this institution for the evaluation of known or suspected cardiac arrhythmias. Before each study, two 12 × 16 cm oval adhesive electrodes (Physio Control Corp.) were attached to each patient in standard defibrillator paddle positions, i.e., left precordial and right infraclavicular positions. The shock advisory system of the Lifepak 200 defibrillator was activated in all patients at the onset of any tachycardia. In 21 consecutive studies performed in 14 patients, the system was activated during normal sinus rhythm. In another 20 studies in 19 patients, the system was activated during atrial pacing at a cycle length of 400 ms.

Results

Arrhythmias occurred during 80 studies in 47 patients. Multiple studies were performed in 24 patients; in 20 patients more than 1 arrhythmia was induced. No arrhythmias were induced during 27 studies in 23 patients. Poor electrode contact prevented the detection algorithm from rendering advice during 3 studies in 2 patients. The final arrhythmia analysis, therefore, included 77 studies in 45 patients (Table I).

The Lifepak 200 defibrillator correctly advised "shock" for 36 of 55 (65%) episodes of sustained VT, all 5 (100%) episodes of VF and the 6 episodes of nonsustained VT that terminated spontaneously after analysis was complete (Table II). "No shock" was correctly advised for 4 episodes of nonsustained VT that terminated spontaneously before analysis was completed. Thus, the sensitivity of the detection algorithm for analyzed VT and VF was 47 of 66 or 71%.

The 19 episodes of sustained VT for which "no shock" was advised occurred in 15 patients. The average cycle length of these tachycardias was longer than that of sustained VT for which "shock" was advised (373 ± 77 ms vs 275 ± 58, $p = 0.0001$) (Figure 1). However, the QRS complexes of these tachycardias were

similar in duration to those of sustained VT for which "shock" was advised (156 ± 35 ms vs 154 ± 28, difference not significant).

The 7 supraventricular arrhythmias were initiated in 4 patients. One automatic atrial tachycardia, 3 episodes of wide QRS complex atrial fibrillation with a rapid ventricular response and 3 cases of narrow QRS complex atrial flutter were observed. The cycle lengths of these tachyarrhythmias varied between 540 and 200 ms. (111 to 300 beats/min). The 3 episodes of wide QRS complex atrial fibrillation occurred in 1 patient with the Wolff-Parkinson-White syndrome. The width of the QRS complex in this patient was 160 ms and the tachycardia cycle length ranged between 260 and 200 ms. (230 to 300 beats/min). The AED advised "shock" in 2 of the 3 episodes. Thus, the overall sensitivity of the detection algorithm for wide QRS complex tachycardias of all types was 49 of 69 or 72%. The remaining 4 cases of supraventricular tachycardia had narrow QRS complexes (80 to 100 ms, mean 85) with cycle lengths ranging between 540 and 300 ms (110 to 200 beats/min). The AED advised "no shock" in all 4 cases. None were rhythms that required electrical cardioversion.

Mode of termination: Ten episodes of VT and 1 episode of atrial fibrillation terminated spontaneously. The remaining arrhythmias (55 VT, 5 VF, 2 atrial fibrillation and 4 supraventricular tachycardia) were sustained and required intervention.

The AED correctly advised "shock" for all 31 ventricular arrhythmias (25 VT, 5 VF) that required direct current electrical countershock because of associated hemodynamic collapse (Table III). The device recommended "shock" for 10 and "no shock" for 19 episodes of VT that were not associated with hemodynamic collapse. Burst rapid ventricular pacing terminated 27 of these arrhythmias. However, 2 of the tachycardias accelerated after rapid ventricular pacing and required electrical countershock for termination. Analysis of these accelerated arrhythmias was not attempted. Statistically significant differences were noted in the mean cycle length of VTs that required electric cardioversion compared with those that were not associated with hemodynamic collapse (261 ± 52 vs 354 ± 74, $p < 0.0001$).

Of the 3 episodes of atrial fibrillation with a rapid ventricular response, 2 required direct current countershock for termination ("shock" was advised for 1 and "no shock" was advised for the other). One episode of atrial fibrillation terminated spontaneously after a "shock" was advised but before it was administered. The 3 episodes of atrial flutter were terminated with atrial pacing. The episode of automatic ectopic atrial tachycardia was not terminated in the laboratory.

Cardioversion: External electrical cardioversion or defibrillation was attempted with the Lifepak 200 defibrillator during 14 episodes of VT and 3 episodes of VF. The device was not used if syncope occurred before it could be activated. Further, only 1 200 joule shock per arrhythmic event was attempted with the Lifepak 200 defibrillator. Additional shocks, when necessary, were administered from a Physio-Control Lifepak 6s defibrillator.

TABLE III Advice for Arrhythmias Associated with Hypotension

Arrhythmia	Shock	No Shock	Sensitivity (%)
VT	26	0	100
Ventricular fibrillation	5	0	100
Wide QRS complex atrial fibrillation	1	1	50
Total	32	1	97

VT = ventricular tachycardia.

The Lifepak 200 AED successfully converted 13 of 14 episodes (93%) of VT and 2 of 3 episodes of VF to normal sinus rhythm. One episode of VT and 1 episode of VF required a second 200 joule countershock from the Lifepak 6s defibrillator to restore sinus rhythm.

Normal sinus rhythm and atrial pacing: The Lifepak 200 shock advisory system was activated during normal sinus rhythm in 14 patients during 21 consecutive studies. The device correctly advised "no shock" in every case. The device also recommended "no shock" during atrial pacing at cycle length 400 ms in 19 patients during 20 studies. The mean QRS complex duration during atrial pacing was 105 ± 21 ms. Further, the device correctly advised "no shock" during 4 episodes of nonsustained VT, which reverted spontaneously to sinus rhythm during analysis and during the 4 episodes of narrow QRS complex supraventricular

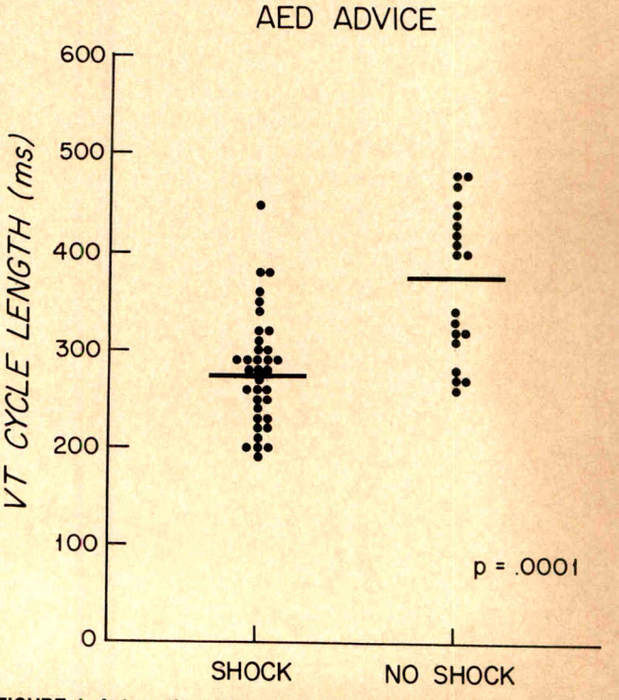

FIGURE 1. Automatic advisory external defibrillator (AED) advice (shock vs no shock) as a function of ventricular tachycardia (VT) cycle length.

tachycardia. Therefore, the specificity of the device for wide QRS complex tachycardias in this study was 100%.

Discussion

Previous studies have evaluated the sensitivity and specificity of various AEDs for VF.[10,14,15] The detection algorithm used in the Lifepak 200 AED is sensitive and highly specific for both VF and VT. In as many as 74% of patients with cardiac arrest, VT precedes VF.[13] Because the automatic advisory defibrillator may be used by family members or other minimally trained persons arriving early at the scene, recognition of VT as well as VF may be important to achieve prompt and effective resuscitation in many patients.

The difference in the sensitivity of the detection algorithm for ventricular arrhythmias associated with hemodynamic collapse (31 of 31, 100%) and those that could be terminated with rapid ventricular pacing is, in part, a reflection of the rate criteria used by the algorithm to classify arrhythmias. The automatic external defibrillator recommended "shock" in 80% (40 of 50) of ventricular arrhythmias with a cycle length <400 ms (150 beats/min) and only 9% (1 of 11) of those with a cycle length ≥400 ms (150 beats/min) (Figure 1). The relative insensitivity of the detection algorithm to slow VT increases its specificity for life-threatening ventricular arrhythmias and reduces the chance of administering inappropriate and potentially harmful shocks to conscious patients who have slower, hemodynamically well-tolerated rhythms. Although QRS complex duration >160 ms is one of the criteria the device uses to sense VT, differences in sensitivity to VT with QRS complex duration >160 ms or <160 ms were small and did not reach statistical significance in this study.

The ability of the AED to terminate VT with a single 200 joule shock (13 of 14 episodes tested, 93%) compares favorably with the experience reported in previous studies.[10,15] In a study using an AED to treat patients with out-of-hospital cardiac arrest, researchers at the University of Iowa reported a 97% conversion rate for VF.[15] In that study, 8 of 26 (31%) of patients converted to asystole, an arrhythmia not encountered following cardioversion in the present study. The comparatively short time to cardioversion in our study probably favored successful conversion to normal sinus rhythm. Our study permitted only 1 AED shock per arrhythmic episode in each patient. It is possible that a second shock from the AED would have converted the 1 failed episode in this study.

In this study the Lifepak 200 detection algorithm demonstrated 100% sensitivity for rapid ventricular arrhythmias associated with hemodynamic collapse. The device was 100% specific for wide complex tachyarrhythmias and was highly effective in converting both VT and VF to normal sinus rhythm with a single 200 joule electrical countershock.

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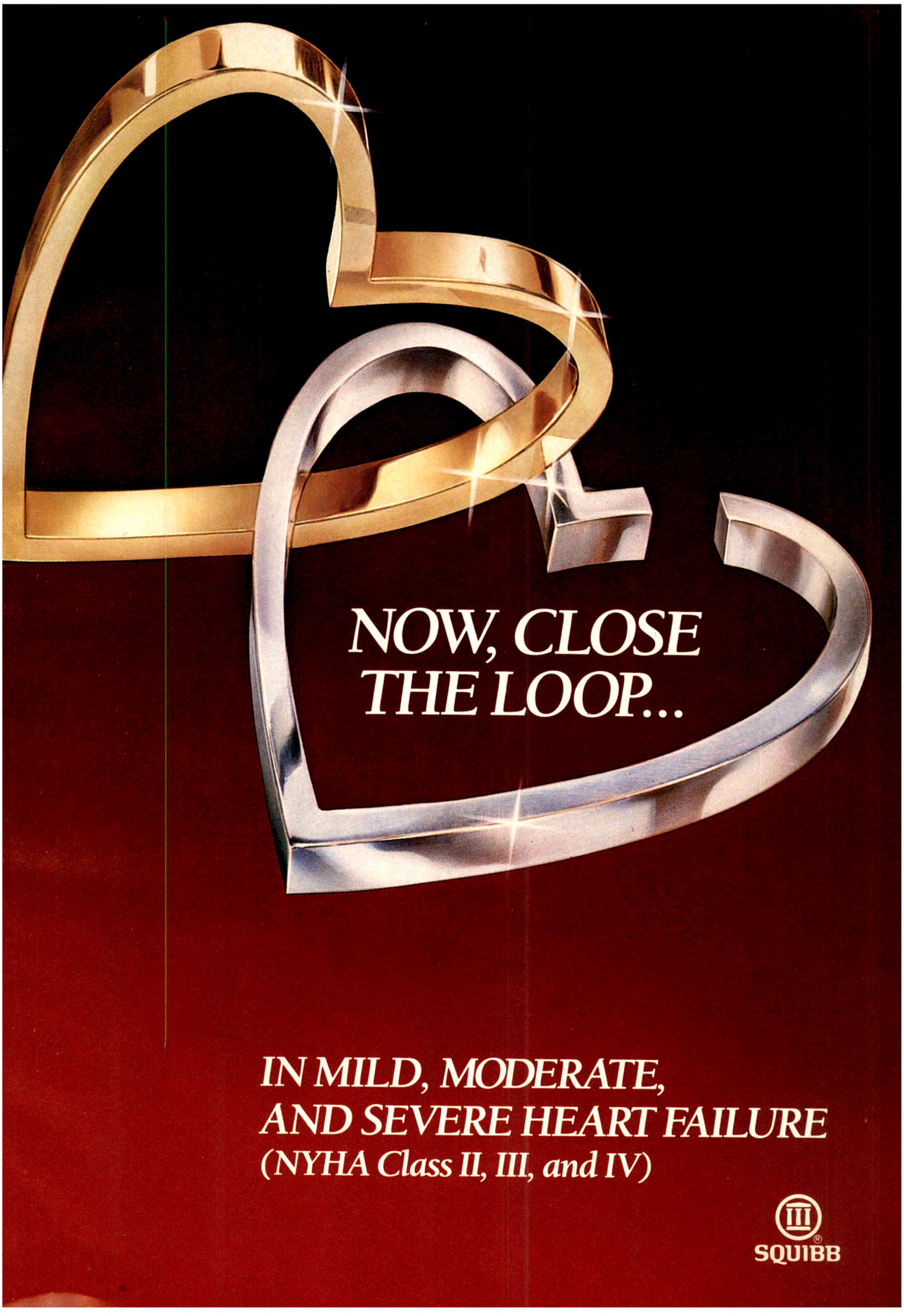
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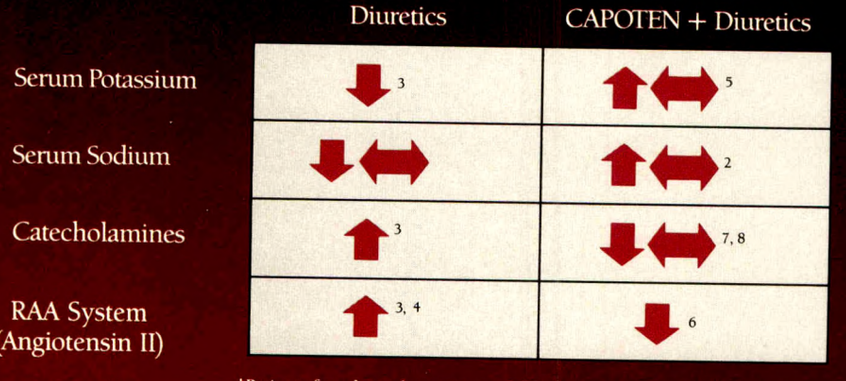

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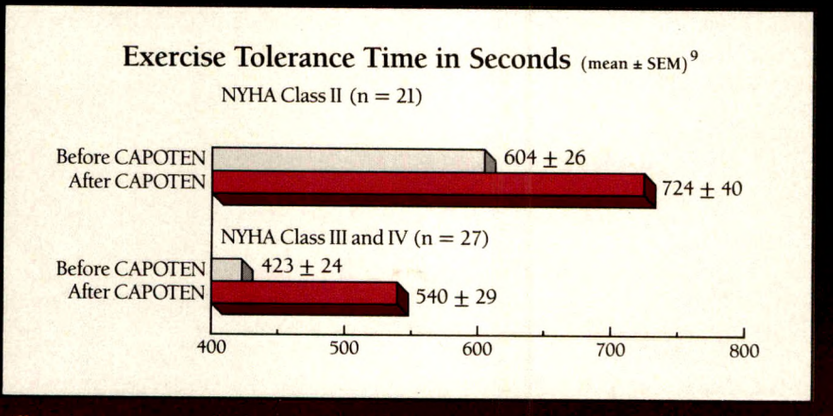

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CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* – Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* – If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension – Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diu and those on severe dietary salt restriction or dialysis. This possibility can be minin by either discontinuing the diuretic or increasing the salt intake about 1 week pr initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators shou administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihyperte agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may l pecially important in supporting blood pressure in patients receiving captopril alo with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive to captopril, but the overall response is less than additive. Therefore, use agents a ing sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blo agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or pota supplements only for documented hypokalemia, and then with caution, since the lead to a significant increase of serum potassium. Use potassium-containing salt s tutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonste anti-inflammatory agents may reduce the antihypertensive effect of captopril, espe in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urin for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studie doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcin potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in nant women. Embryocidal effects and craniofacial malformations were observed i bits. Therefore, captopril should be used during pregnancy, or for patients lik become pregnant, only if the potential benefit outweighs the potential risk to the Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution wh ministering captopril to a nursing woman, and, in general, nursing should be interr

Pediatric Use: Safety and effectiveness in children have not been established altl there is limited experience with use of captopril in children from 2 months to 15 y age. Dosage, on a weight basis, was comparable to that used in adults. CAPC (captopril) should be used in children only if other measures for controlling bloo sure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials inv approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Re sufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 pa

Hematologic – Neutropenia/agranulocytosis has occurred (see WARNINGS) mia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash, (usually maculopapular, rarely urticarial), often with pr and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depend renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, withou in about 2 of 100 patients. A reversible associated pemphigoid-like lesion photosensitivity, have also been reported. Angioedema of the face, mucous memt of the mouth, or of the extremities in about 1 of 1000 patients – reversible on disc uance of captopril therapy. One case of laryngeal edema has been reported. Flush pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur; see WARNINGS and PRECAUT [Drug Interactions] for discussion of hypotension on initiation of captopril th Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pe myocardial infarction, Raynaud's syndrome, and congestive heart failure each in of 1000 patients.

Dysgeusia – Approximately 2 to 4 (depending on renal status and dose) of 100 p developed a diminution or loss of taste perception; taste impairment is reversib usually self-limited even with continued drug use (2 to 3 months). Gastric irri abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appea creased frequency compared to placebo or other treatments used in controlled tr

Altered Laboratory Findings: Elevations of liver enzymes in a few patients alt no causal relationship has been established. Rarely cholestatic jaundice, and hepatoc injury with or without secondary cholestasis, have been reported. A transient ele of BUN and serum creatinine may occur, especially in volume-depleted or renova hypertension patients. In instances of rapid reduction of longstanding or severe vated blood pressure, the glomerular filtration rate may decrease transiently, also re in transient rises in serum creatinine and BUN. Small increases in serum pot concentration frequently occur, especially in patients with renal impairmer PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume exp with an I.V. infusion of normal saline is the treatment of choice for restoration of pressure. Captopril may be removed from the general circulation by hemodialys

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be tak hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosag be individualized; see DOSAGE AND ADMINISTRATION section of package for detailed information regarding dosage in hypertension and in heart failure. B CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustme recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose p 100 tablets. (J

References:

1. The Captopril Multicenter Research Group I: Am Heart J 110:439-447, 1985. 2. Dzau VJ, Hollenberg NK: Ann Intern Med 100:777-782, 1984. 3. Packer M: Prim Cardiol, August 1987, pp 100-107. 4. Ikram H, Chan W, Espiner EA, et al: Clin Sci Mol Med 59:443-449, 1980. 5. Cleland JG, Dargie HJ, East BW, et al: Eur Heart J 6:681-688, 1985. 6. Dzau VJ: Drug Th September 1986, pp 57-68. 7. Mettauer B., Rouleau J-L, Bichet D, Circulation 73:492-502, 1986. 8. Cleland JGF, Dargie HJ, Hodsman GI Br Heart J 52:530-535, 1984. 9. Captopril Multicenter Research C J Am Coll Cardiol 2:755-763, 1983.

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Determinants of Survival in Patients with Malignant Ventricular Arrhythmia Associated with Coronary Artery Disease

STEVEN LAMPERT, MD, BERNARD LOWN, MD, THOMAS B. GRABOYS, MD, PHILIP J. PODRID, MD, and CHARLES M. BLATT, MD

The long-term survival data in patients with coronary artery disease and a history of malignant ventricular arrhythmia, defined as noninfarction ventricular fibrillation (VF) or hemodynamically compromising ventricular tachycardia (VT) followed for up to 9 years, were analyzed. In this group of 161 patients there was a total of 57 deaths, of which 35 (63%) were sudden. Life-table analysis demonstrated a 10% sudden death rate for all patients in the first year and a 7% annual rate in the subsequent 4 years. In patients managed noninvasively, the overall mortality rate was 27% over 9 years, or 3% per year. Suppression of ventricular tachycardia on both ambulatory monitoring and exercise testing was associated with improved survival. In patients evaluated by electrophysiologic testing the sudden death rate was 1.4% per year over an average of 5 years. This survival rate was not different compared with the noninvasive group ($p = 0.09$). Measures of left ventricular dysfunction and the frequency of ventricular arrhythmia before and after drug therapy were associated with a risk of sudden cardiac death by univariate analysis. Multivariate regression analysis identified 4 variables as independent predictors of sudden cardiac death: rales ($p = 0.009$), the number of runs of VT during exercise testing while receiving antiarrhythmic drug therapy ($p = 0.0003$), a history of congestive heart failure ($p = 0.0009$) and the number of premature beats on Holter monitoring ($p = 0.01$). These findings support the concept that suppression of repetitive arrhythmia on Holter monitor and exercise testing is a marker for improved survival among patients with malignant ventricular arrhythmia. However, in the coronary population at high risk of sudden cardiac death, ventricular function is the most powerful predictor of survival and, when severely depressed, the control of ventricular arrhythmia does not significantly improve outcome.

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Preventing sudden cardiac death in patients with coronary artery disease remains a clinical challenge.[1] Advances in this area during the past 2 decades have comprised a diversity of approaches including cardiopulmonary resuscitation, numerous new antiarrhythmic drugs, electrophysiologic identification of the patient at risk, automatic implantable defibrillators and cardioverters, and surgical ablation of the arrhythmic focus. Perhaps the most significant advance relates to a conceptual change, namely, that the patient at risk is identifiable and that sudden death may be preventable.[1]

Current treatment of patients threatened with sudden cardiac death is based on 2 hypotheses. First, sudden death is due to ventricular fibrillation (VF), often heralded by ventricular tachycardia (VT). Second, elimination of repetitive ventricular arrhythmia, whether induced electrophysiologically or occurring spontaneously, protects against these lethal events.[2,3] Through our efforts, as well as those of other investigators, it was demonstrated that the control of complex ventricular ectopic activity based on a noninvasive evaluation or the suppression of their provocation by programmed electrical stimulation is associated with improved survival in high-risk patients.[2,4,5]

A number of relevant questions concerning the management of these patients remain to be answered.

From the Cardiovascular Laboratories, Department of Nutrition, Harvard School of Public Health, and the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, This study was supported in part by grant HL-07776 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, and The Rappaport International Program in Cardiology. Manuscript received May 21, 1987; revised manuscript received and accepted December 4, 1987.

Address for reprints: Steven Lampert, MD, Harvard School of Public Health, Lown Cardiovascular Laboratory, 221 Longwood Avenue, Boston, Massachusetts 02115.

TABLE I Clinical Variables of 161 Patients with Malignant Ventricular Arrhythmia

Clinical Variable	
Age (yr)*	58 ± 11
Male:female ratio	5:1
Myocardial infarction	127 (79%)
Arrhythmia characteristics	
Ventricular fibrillation	86 (53%)
Ventricular tachycardia	75 (47%)
No. of unsuccessful drug trials*	2.5 ± 1.8
Left ventricular function	
Left ventricular ejection fraction*	0.36 ± 0.19
Cardiomegaly	78 (49%)
Clinical congestive heart failure	72 (45%)

* Values are mean ± standard deviation.

Are patients who respond to antiarrhythmic drugs different from those in whom complex ventricular arrhythmias persist despite therapy? What clinical variables, in addition to arrhythmia, predict survival? In subjects with malignant ventricular arrhythmias, what degree of arrhythmia elimination is necessary to ensure protection? This report addresses these questions and updates earlier studies.

Methods

Patients: One hundred sixty-one survivors of either noninfarction VF or sustained VT associated with syncope or presyncope were referred for management and constitute the study group. All patients had coronary artery disease evidenced by cardiac catheterization, a documented myocardial infarction or angina. Clinical investigations were performed at the Brigham and Women's Hospital or the Cardiovascular Laboratories at the Harvard School of Public Health. Eighty-six patients were referred after at least 1 episode of VF, of whom 30 patients (34%) had 2 or more cardiac arrests. The remaining 75 patients had sustained hemodynamically compromising VT with either syncope or presyncope. In 51 patients (68%), the symptomatic tachyarrhythmia occurred more than once. The patients' clinical characteristics are listed in Table I.

Evaluation procedures: The evaluation of these patients has been described in previous studies.[2] Patients were admitted either to a coronary care unit or a cardiac unit with telemetry capabilities. Antiarrhythmic drugs were stopped whereas digoxin and β-adrenergic blocking agents were continued when indicated. In 130 patients (82%) antiarrhythmic drugs were stopped without sequelae; runs of nonsustained VT were untreated during this initial phase. Continuous antiarrhythmic drug therapy to prevent recurrent VF or sustained symptomatic VT was required in 23 patients (14%). The remaining 8 patients (4%) were considered medically unstable and continued receiving antiarrhythmic drugs. The baseline, or control phase of arrhythmia evaluation, included 48 hours of ambulatory monitoring, an exercise tolerance test and a radionuclide ventriculogram. These were carried out after a drug washout period equal to 5 half-lives of any antiarrhythmic drug.

Ambulatory monitoring: Monitor data analysis was performed using a cardiac arrhythmia analyzer (American Optical Corportion) and, more recently, a CAMSCAN 7200 system. Both devices employ a tape playback system that allows 60× or 120× real-time analysis of 24-hour cassettes (the methods have been previously described).[6] Data reduction of ventricular premature beat activity was carried out by qualitative analysis and adhered to the following classification of ventricular premature beats[7]: grade 0, no ventricular premature beats; grade 1, occasional (<30/hr; A, <1/min and B, >1/min); grade 2, frequent ventricular premature beats (>1/min); grade 2, frequent ventricular premature beats (>1/min or 30/hr); grade 3, multiform ventricular premature beats; grade 4, repetitive ventricular premature beats (A, couplets and B, salvos or ventricular tachycardia). Semiautomated data reduction permits quantification of total ventricular premature beats and repetitive forms. Ten percent of all tapes were randomly chosen for quality control.[6]

Exercise stress testing: Testing was performed adhering to a Bruce protocol[8] on a motorized treadmill and has been previously described.[9,10] An electrocardiographic tracing was continuously displayed on an oscilloscope. A permanent continuous record was obtained on a Trendscriber[11] and on a standard electrocardiogram strip chart recorder that inscribed 3 simultaneous leads. Exercise was maximal and symptoms limited, discontinued only when the patient experienced progressive dyspnea, intensifying angina pectoris, or sustained atrial or ventricular tachyarrhythmia. Emergence of ST-segment depression, ventricular premature beats, couplets or episodic ventricular tachycardia did not constitute a reason for terminating the test. Quantification and grading of total ventricular premature beats took place during the control, exercise and recovery periods.[11]

The determination of a methodologic approach for selecting the appropriate antiarrhythmic drug was based on the data acquired during the baseline evaluation. The decision was between noninvasive or electrophysiologic testing. The patient underwent a noninvasive evaluation if monitoring demonstrated grade 2 ventricular premature beats for >50% of the hours and grade 4B arrhythmia for at least 3 hours per day or at least 2 ventricular premature beats per minute provoked by exercise. Electrophysiologic testing was used if this level of arrhythmia was absent or the ventricular arrhythmia was not reproducible from one 24-hour period to the next. Of the 161 patients, 43 (27%) required electrophysiologic testing to guide antiarrhythmic drug therapy, whereas in the remaining 118 patients repeated ambulatory monitoring and exercise testing provided information for drug selection.

Electrophysiologic testing was based on the following protocol. Under fluoroscopic guidance, a 6 Fr hexapolar electrode catheter was inserted percutaneously into the left subclavian vein and positioned at the right ventricular apex. Programmed electrical stimulation

was performed, using up to 3 successive extrastimuli with a pulse width of 5 ms at energies of 2 and 3 times the mid-diastolic threshold, as previously reported.[12] Studies were carried out during both sinus rhythm and ventricular pacing at a cycle length of 500 ms. The endpoint of stimulation was the induction of reproducible nonsustained VT, defined as 3 or more ventricular premature beats (≥ 30 seconds) after the last provoked extrastimulus. To be considered reproducible, the endpoint had to be provoked in 2 of 3 trials at the same coupling cycle and with the same stimulus energy. All patients who required electrophysiologic testing underwent at least 1 baseline study without receiving any antiarrhythmic agent. The purpose of the electrophysiologic study was to induce an arrhythmia against which antiarrhythmic drug effect could be tested.[13]

Antiarrhythmic therapy: The selection of the discharge drug program was based on the results of either the noninvasive or invasive drug evaluations. Both methods used a structured protocol for antiarrhythmic drug selection, which has been previously described.[14-16] The evaluation consisted of 2 phases. Phase 1 covered acute drug testing and phase 2 dealt with short-duration maintenance therapy with a selected antiarrhythmic agent.

In phase 1, a single large oral dose of an antiarrhythmic agent was administered orally after a 30-minute control monitoring period. Thereafter, hourly counts of ventricular ectopic beats were hand tabulated, using programmed trendscription.[11] The patient also was exercised on a bicycle ergometer before the administration of the drug and hourly thereafter. A separate tabulation was made for exercise-induced arrhythmia, comparing the hourly tests after the administration of the drug with the initial bicycle exercise test. Sampling of blood for drug concentration was carried out hourly to assure that a so-called therapeutic blood concentration was achieved. The objective of therapy was elimination of advanced grades of ventricular premature beats (grades 4A and 4B) and reduction by 50% of frequent ventricular premature beats. Acute drug tests were performed daily with different agents, permitting a 24-hour washout period between drugs.

In phase 2, which continued for 48 to 96 hours, the aim was to assess antiarrhythmic drug efficacy and gauge drug tolerance with a dosing program simulating long-term drug maintenance. Drugs that proved effective during phase 1 were used, including agents that could not be tested acutely. Drugs either with a long half-life or with electrophysiologically active metabolites underwent phase 2 testing only. The oral dosing schedule during phase 2 was guided by the pharmacokinetic properties of the selected antiarrhythmic agent. Drug effect was assessed by means of 24-hour Holter monitoring and maximal exercise stress testing. An effective response during the noninvasive assessment required fulfillment of the following criteria: (1) total elimination of grade 4B ventricular premature beats; (2) reduction of >90% in grade 4A ventricular beats; (3) >50% reduction in total number of ventricular premature beats. These criteria had to be met with both 24-hour Holter monitoring and exercise stress testing. When electrophysiologic testing was used, drug effectiveness was defined as the inability to provoke nonsustained VT defined as ≥3 beats.

The drug best tolerated during phase 2 studies was selected for long-term therapy. When a single drug failed to control the arrhythmia, 2 partially effective drugs (based upon either phase 1 or phase 2 testing) were combined and reevaluated. Even if a single agent was effective for patients with recurrent VF, 2 antiarrhythmic drugs were generally used to provide a so-called fail-safe program of drug protection.[16] Each drug had been independently evaluated and the combined therapy was evaluated prior to discharge.

Follow-up: Patients were followed for an average of 31.5 ± 26 months (range 0.13 to 107.5). Follow-up began on the date of hospital discharge and ended on the date of the patient's death, withdrawal because of loss to follow-up (1 patient at 88 months), or termination of the study.

Definitions and data analysis: The type of arrhythmia evaluation and degree of arrhythmia control on the final drug program divided the population into 4 groups. In 61 (52%) of the 118 noninvasively evaluated patients, the ventricular arrhythmia was considered controlled if, during 24 hours of ambulatory monitoring, VT was limited to no more than 2 runs (each lasting less than 6 beats) and exercise testing failed to provoke VT (≥3 cycles). If either ambulatory monitoring or exercise testing failed to meet these conditions, or if the patient was for any reason unable to undergo either evaluation, the patient was considered not controlled (n = 57, 48%). In 21 of the 43 patients evaluated by the invasive method, 3 extrastimuli failed to induce any VT (3 or more beats) while the patient was receiving an antiarrhythmic agent. These patients were considered controlled. In the remaining 22 patients, 10 were discharged after being prescribed medicine that either slowed the VT rate or made the arrhythmia more difficult to induce. In 12 patients, another antiarrhythmic agent was empirically added and not evaluated by electrophysiological testing. For analysis purposes, these 22 patients were considered noncontrolled by electrophysiologic testing.

Sudden cardiac death was defined as death within 1 hour of onset of the terminal event. Patients who were found dead but known to be alive and free of symptoms within the previous 24 hours were considered to have died suddenly. Cardiac fatality included sudden death and death due to progressive circulatory failure.

Continuous data are expressed as mean ± standard deviation. The association between the analyzed variables and sudden cardiac death was determined with univariate statistical methods. Actuarial survival curves for sudden death and cardiac death were constructed using the product-limit method (Kaplan-Meier).[17] Differences in mortality curves for analyzed variables were compared using the Breslow modification of the generalized Wilcoxon test.[18]

Multivariate regression analysis using the Cox proportional hazards linear model with the Breslow modification for tied data was performed to identify variables with significant predictive value for sudden cardiac death.[19] All variables with a univariate predictive value of at least p <0.10 were included in the regression model. When values were missing because either a baseline or final arrhythmia evaluation was not performed, median values (obtained from the univariate analysis) were substituted in the multivariate analysis. Variables were considered predictive of sudden cardiac death when the p value of the chi-square analysis was <0.05.

Results

Survival: Actuarial survival curves for sudden death and cardiac death for the entire study group are presented in Figure 1. There was a total of 57 deaths, of which 56 were due to a cardiac event. Thirty-five of the cardiac deaths (63%) were sudden. The actuarial sudden death rates at 1, 2 and 5 years were 10 ± 2%, 13 ± 2% and 34 ± 6%, respectively.

Determinants of survival: When tested by univariate analysis, many variables were associated with sudden cardiac death (Table II). A number of measures of left ventricular dysfunction as well as frequency of ventricular premature beats during the baseline ambulatory monitoring were closely associated with sudden death. Patients unable to undergo a baseline (drug-free) evaluation were more likely to die suddenly, compared with patients who could safely discontinue antiarrhythmic drugs. The lack of arrhythmia suppression at discharge from the hospital also was associated with sudden death, as was the frequency of ventricular premature beats during the discharge exercise testing and Holter monitoring.

Multivariate regression analysis identified 4 variables as independent predictors of sudden cardiac death in the entire cohort: rales during the initial physical examination (p = 0.009), the number of runs of VT on the discharge exercise test (p = 0.0003), a history of congestive heart failure (p = 0.0009) and the number of hours of frequent (grade 2) ventricular premature beats on the discharge Holter monitor (p = 0.01). All the other univariate factors failed to provide additional independent predictive value. When analysis was limited to the 118 patients whose therapy was based upon the noninvasive evaluation, the same 4 independent predictors of sudden death were identified.

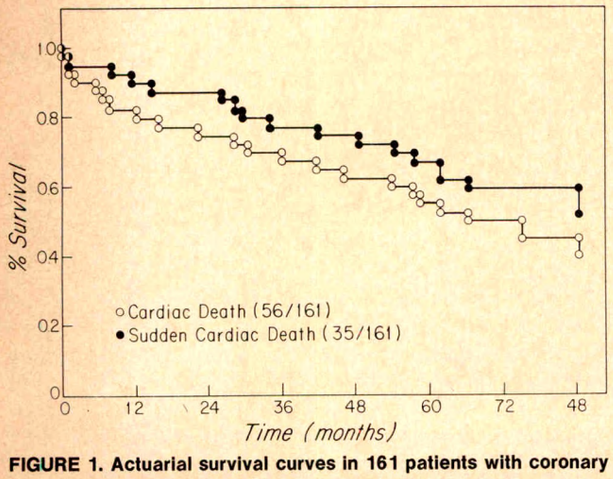

FIGURE 1. Actuarial survival curves in 161 patients with coronary disease and malignant ventricular arrhythmia followed for an average of 31.5 months.

TABLE II Univariate Predictors of Sudden Death

Variable	p Value
Age	NS*
Arrhythmia diagnosis	NS
Left ventricular function	
H/O CHF	<0.018
Cardiomegaly	NS
S_3 on physical examination	<0.049
Ejection fraction	<0.002
Rales	<0.056
Baseline arrhythmia	
discontinue therapy†	<0.02
grade 2	0.039
grade 3	0.044
grade 4a	NS
grade 4b	0.068
Amount of arrhythmia at discharge	
Holter monitor	
grade 2	0.014
grade 3	0.039
grade 4a	NS
grade 4b	NS
Exercise testing	
grade 2	0.085
grade 4a	0.076
grade 4b	0.106
Arrhythmia controlled at discharge	0.029

* NS (not significant) when p >0.10; † discontinue therapy = when drugs can be stopped without sustained tachyarrhythmia occurring.
H/O CHF = history of congestive heart failure.

Survival by method of evaluation and arrhythmia control: Patients evaluated by noninvasive methods experienced an overall sudden death rate of 27% during a 9-year (3%/yr) follow-up period as compared with 7% in the group managed by electrophysiologic testing and followed for an average of 5 years (1.4%/yr). The difference in the actuarial survival rate did not reach statistical significance (p = 0.09). There were 3 sudden cardiac deaths in the invasively managed group. Two occurred within 8 months of discharge and 1 at 26 months. The 2 groups were clinically similar with respect to prior history, initial physical examination and left ventricular function. The major difference was in the amount of baseline arrhythmia, with the invasive group being nearly free of frequent or reproducible higher grades of ventricular arrhythmia during both Holter monitoring and exercise testing. Although the mean left ventricular ejection fraction was slightly higher in the group undergoing electrophysiologic testing (41.5 vs 33.8%, p = 0.053), other indexes of left ventricular function were not different.

The percentage of patients with a history of congestive heart failure (43 vs 46%), cardiomegaly by chest x-ray (39 vs 53%) and with an ejection fraction below 40% (51 vs 62%) were not significantly different between the invasive and noninvasive groups.

The actuarial sudden death rates in the controlled (n = 61) and noncontrolled (n = 57) groups, based on the noninvasive evaluation, are shown in Figure 2. The difference in survival between the 2 groups is significant at the $p < 0.02$ level. The largest difference occurred during the first year after discharge, when 19% of patients in the noncontrolled group died suddenly compared with 5% in the controlled group. At 5 years, the sudden death rates were 48 ± 9% and 29 ± 8%, respectively.

Patients evaluated by electrophysiologic testing had excellent survival rates. Survival was not related to the presence or absence of inducible nonsustained VT on the discharge drug program. Patients who were discharged with inducible nonsustained VT had an overall survival of 86% compared with 100% in patients free of inducible arrhythmia (difference not significant).

In the entire cohort of patients, all Lown grades of ventricular arrhythmia were reduced during exercise testing and ambulatory monitoring. The reduction during exercise testing was associated with fewer sudden cardiac deaths (Table III). The median reductions in Lown grades 2, 4A and 4B during ambulatory monitoring were 90, 95 and 100%, respectively. For exercise tolerance testing, the median percentage reductions were 96, 100, and 100% for Lown grades 2, 4A and 4B.

Comparison of the controlled and noncontrolled groups: The baseline clinical characteristics of the controlled and noncontrolled groups are compared and summarized in Table IV. The major difference between the 2 groups was the degree of left ventricular impairment. Clinical signs of left ventricular impairment were found more often in the noncontrolled group. When the 2 groups were classified according to the left ventricular ejection fraction, 33% of the controlled group had left ventricular dysfunction (left ventricular ejection fraction <30%), compared with 51% of the noncontrolled group ($p = 0.08$). Thus, ventricular arrhythmia was suppressed more often in patients without left ventricular impairment. The frequency of ectopic activity or the grade of ventricular arrhythmia during baseline studies was not correlated with the degree of left ventricular impairment in either group.

The interaction between left ventricular function and ventricular arrhythmia suppression was evaluated by stratifying the cohort into 4 groups. The patients were initially stratified as having normal or abnormal left ventricular function based on an ejection fraction above or below 30% and, within each group, dichotomized according to the degree of control of the ventricular arrhythmia. The results are presented in Figure 3. When the left ventricular ejection fraction was >30%, controlling ventricular arrhythmias were associated with improved survival ($p = 0.05$). When

TABLE III Comparison of the Percent Reduction* of Lown Grades of Ventricular Arrhythmia in Survivors Versus Nonsurvivors

	Nonsurvivors		Survivors		
	Ave	(n)†	Ave	(n)	p Value
Monitoring					
Reduction grade 2 (%)	40	22	40	72	NS
Reduction grade 4A (%)	51	22	56	76	NS
Reduction grade 4B (%)	85	16	65	59	NS
Exercise testing					
Reduction grade 2 (%)	10	15	26	60	0.002
Reduction grade 4A (%)	79	12	84	44	NS
Reduction grade 4B (%)	80	11	96	30	0.07

* A negative percent reduction indicates an increase in the amount of ventricular arrhythmia.

† Patients free of a particular ventricular arrhythmia grade during baseline evaluation are not included in the analysis, because a percent reduction is not calculable.

Ave = average reduction; NS = not significant.

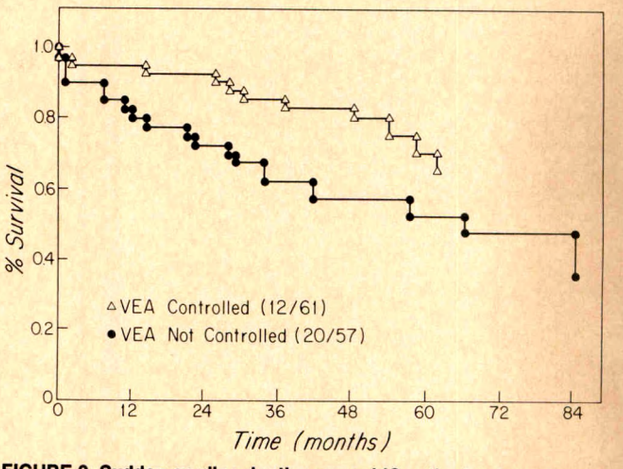

FIGURE 2. Sudden cardiac death among 118 patients whose therapy was guided by a noninvasive evaluation. This was based upon ventricular arrhythmia control (n = 61) or no control (n = 57) at the time of discharge from the hospital.

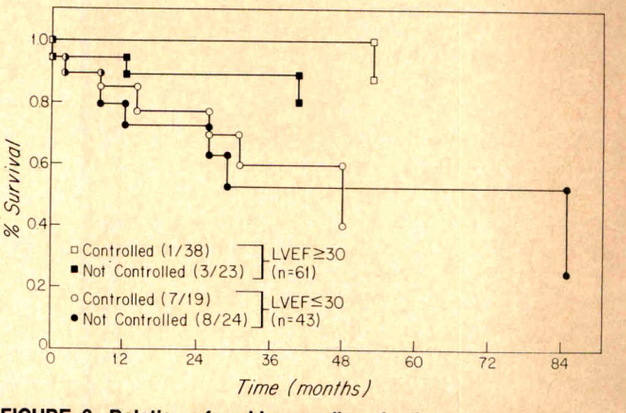

FIGURE 3. Relation of sudden cardiac death to left ventriuclar function and arrhythmia control.

TABLE IV Comparison of Clinical Variables in the Arrhythmia Controlled and Noncontrolled Groups

Clinical Variables	Final Arrhythmia Status		p Value
	Controlled	Noncontrolled	
Age	58 ± 9	58 ± 12	NS
Males (%)	87	81	NS
SH (%)	41	34	NS
CHF (%)	36	55	0.017
Cardiomegaly by CXR (%)	38	63	0.002
H/O VF (%)	57	50	NS
H/O VT (%)	52	61	NS
LVEF (%)	40 ± 20	32 ± 18	<0.05
Number of previous drugs	2.5	2.5	NS
Baseline evaluation			
Ambulatory monitoring			
Grade 2 (hr)	14 ± 10	11 ± 10	NS
Grade 3 (hr)	16 ± 9	13 ± 10	NS
Grade 4A (hr)	10 ± 9	8 ± 9	NS
Grade 4B (hr)	4 ± 6	4 ± 6	NS
Exercise testing			
Exercise duration (min)	6 ± 3	6 ± 3	NS
Peak heart rate (beats/min)	141 ± 25	138 ± 27	NS
Peak systolic BP (mm Hg)	152 ± 31	141 ± 28	NS
ST-segment depression* (mm)	2 ± 1	2 ± 1	NS
VPB (per test)	71 ± 108	112 ± 151	NS
Couplets (per test)	8 ± 22	7 ± 11	NS
VT runs (per test)	2 ± 7	2 ± 5	NS

* >1 mm J-point depression in lead V_5 in the absence of digoxin therapy or resting ST-segment shift.

BP = blood pressure; CAD = coronary artery disease; CHF = congestive heart failure; CXR = chest x-ray; NS = not significant; SH = systemic hypertension; VF = ventricular fibrillation; VPB = ventricular premature beats; VT = ventricular tachycardia.

severe left ventricular dysfunction was present, controlling arrhythmia did not affect the sudden death rate.

Discussion

The present study corroborates earlier findings that the control of advanced grades of ventricular premature beats with antiarrhythmic drugs is associated with improved survival in patients with coronary artery disease presenting with life-threatening ventricular arrhythmias. In these 161 patients, prognosis was related to the severity of left ventricular dysfunction and the frequency of VT during antiarrhythmic drug therapy.

In an earlier report from our laboratory, the annual rate of sudden cardiac death in a heterogeneous population was 2.3% when the objective of therapy aimed at the total elimination of VT salvos and R-on-T ventricular premature beats.[2] In the present study, a nearly similar result was achieved with less rigorous control of ventricular ectopic activity in a population with coronary artery disease. The presence of >2 salvos of nonsustained ventricular tachycardia (<6 beats) was associated with a sudden cardiac death rate of approximately 5% per year, compared to 3.4% when all couplets and runs of VT were eliminated. Although elimination of VT salvos remains a valid therapeutic objective,[4] total abolition of arrhythmia in these high-risk patients may not be necessary to optimize prognosis.

The state of the left ventricular function has been identified as an important predictor of survival in a variety of patient populations. Swerdlow and co-workers[5] found that the New York Heart Association functional classification was a strong predictor for sudden death in a group of patients with malignant ventricular arrhythmias evaluated by electrophysiologic testing. In a long-term follow-up study of resuscitated victims of out-of-hospital cardiac arrest, Goldstein et al[20] suggested that the major determinant of survival was left ventricular dysfunction. Bigger and co-workers[21] followed 766 survivors of acute myocardial infarction and demonstrated that a left ventricular ejection fraction of <30% was an independent predictor of survival, with the mortality rate increasing further in the presence of either frequent or high-grade ventricular arrhythmias.[21-23] We also found that the left ventricular function was the strongest predictor of survival in patients with malignant ventricular arrhythmia. When patients were stratified according to left ventricular function, the control of ventricular arrhythmia was most beneficial in patients with an ejection fraction >30.

We learned that estimates of left ventricular function and the amount of ventricular arrhythmia during antiarrhythmic drug therapy were the strongest predictors of survival. The presence of rales at the time of admission had the highest chi-square value of all variables entered into the logistic regression equation. The number of runs of VT during the final exercise tolerance test was the next most important predictor of sudden death. This conclusion is important because exercise tolerance testing is not routinely used to guide antiarrhythmic drug therapy. As a therapeutic approach for the general population, whether ventricular arrhythmia during exercise tolerance testing adds independent prognostic information beyond other exercise parameters has been a controversial issue. Few investigators use this noninvasive procedure to assess antiarrhythmic drug effectiveness in patients with ventricular arrhythmias. Over the past decade we have used this testing method as an integral part of our antiarrhythmic drug evaluation and found that, in 15% of drug trials, exercise testing exposes arrhythmia which was not present on the therapeutic ambulatory monitor. It is possible that differences in survival among different institutions are related to whether exercise testing is used to determine drug effectiveness.

Sufficient evidence has now accrued to support the hypothesis that suppression of ventricular premature beats in patients who have survived sudden cardiac death or symptomatic VT by an effective antiarrhythmic program is associated wtih enhanced long-term survival. It is possible that a positive response to antiarrhythmic therapy merely identifies a subset of patients who have a lower risk of dying suddenly and the therapy does not truly "protect" the patient. If this is the case, then survival in these patients is unrelated to the drug therapy. Our group[24] recently examined the recurrence of clinical arrhythmia after cessation of an effective drug program. Among 24 patients who un-

derwent antiarrhythmic drug withdrawal, there was a 50% recurrence of either cardiac arrest or sustained ventricular tachycardia. This mortality rate, after discontinuing drug therapy, suggests that patients with a history of malignant ventricular arrhythmia are always at risk of recurrence and that antiarrhythmic therapy effectively protects these high-risk patients.

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Effect of Behavior State on Caffeine's Ability to Alter Blood Pressure

GWENDOLYN A. PINCOMB, PhD, WILLIAM R. LOVALLO, PhD,
RICHARD B. PASSEY, PhD, and MICHAEL F. WILSON, MD

Caffeine use during exposure to mental stress is an extremely common occurrence. Because both have been shown to alter blood pressure (BP) and its underlying hemodynamic mechanisms, the potential exists for additive or even synergistic effects. Changes in heart rate, BP and noninvasive thoracic impedance measures of left ventricular function were examined in young men (ages 20 to 36) at rest and during a demanding behavioral task performed 40 minutes after predosing with caffeine (3.3 mg/kg, equivalent to 2 to 3 cups of coffee) or placebo in a double-blind crossover design. All subjects were healthy young men without history of cardiovascular disease, regular use of nicotine, recreational or prescription drugs or caffeine intolerance. Caffeine abstinence was required for 12 hours before each test session. Systolic and diastolic BP were elevated by both caffeine and the behavioral task alone ($p < 0.01$ for each); when combined, caffeine's pressor effects were additive to those of the behavioral task. However, caffeine's pressor effect was produced by different mechanisms depending on the behavioral state. Caffeine increased systemic vascular resistance ($p < 0.01$) under resting conditions, but it enhanced cardiac output ($p < 0.01$) during behavioral arousal associated with the task. The combined influence of caffeine and the task increased the number of men in whom peak systolic BP reached hypertensive levels, and also synergistically increased cardiac minute work ($p < 0.01$) and the rate-pressure product estimate of myocardial oxygen demand ($p < 0.05$). Implications of these findings are discussed for longstanding theoretical disputes regarding caffeine, its health consequences, and for methodologic issues in behavioral and clinical studies.

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Caffeine's effects on cardiovascular regulation in humans, which have been questioned for at least a century,[1] remain a subject of controversy among scientists, physicians and the lay public. Early theoretical disputes concerned whether caffeine elevates blood pressure (BP) by: (1) enhancing vasoconstriction and thus vascular resistance, or (2) producing cardiac stimulation of rate, contractility or both, which then increase cardiac output sufficiently to overcome enhanced vasodilation. No consensus yet exists regarding these mechanisms, because the few previous studies involved a small number of normal volunteers or patients and lacked a placebo-controlled condition.[2–5]

The mechanism of caffeine's pressor effect has important health implications. Caffeine-induced vasoconstriction might accelerate the development of systemic hypertension and its associated vascular, cardiac and renal pathology. Mild cardiac stimulation, if accompanied by vasodilation, might improve circulatory capacity with benefits that outweigh the risks of modestly elevated BP. Thus far prospective studies relating caffeine use to cardiovascular disease and mortality have yielded inconclusive findings.[6–11] A recent study refined the estimates of daily caffeine use by obtaining updated information about coffee con-

From the Veterans Administration Medical Center and the Departments of Psychiatry and Behavioral Sciences, Pathology and Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma. This research was supported by funds from the Medical Research Service of the Veterans Administration, Washington, D.C. Manuscript received September 18, 1987; revised manuscript received December 7, 1987, and accepted December 8.

Address for reprints: Gwendolyn A. Pincomb, PhD, Veterans Administration Medical Center, Behavioral Sciences Laboratories–151A, 921 Northeast 13th Street, Okalhoma City, Oklahoma 73104.

sumption at 5-year intervals[12] and reported a significant elevation in relative risk of 2.5 for subsequent coronary artery disease in recent heavy coffee drinkers (≥5 cups daily), even after adjustment for the effects of age, systemic hypertension, current cigarette smoking and baseline serum total cholesterol levels.

In most placebo-controlled designs, acute administration of caffeine or coffee leads to systolic and diastolic BP elevations, and may also slightly decrease heart rate (HR). A few investigators suggest that a rapid development of tolerance during long-term caffeine administration eliminates sustained elevations in BP; and tolerance may at least partially account for discrepant epidemiologic findings.[13] However, the duration of tolerance is apparently brief, since habitual caffeine use does not usually alter the BP response magnitude to caffeine after only a 12-hour abstinence.[14–17]

Caffeine's actions are undoubtedly complex. One hypothesis is that caffeine's effects are modified by psychologic/behavioral stressors, because both affect common organ systems and both may occur simultaneously under natural conditions. Few available studies examined this hypothesis in humans. Caffeine appeared to increase BP, but not HR in early studies concerning caffeine's effects on psychomotor speed and accuracy.[18] The administration of caffeine before performance of a mental arithmetic task did not change HR, but resulted in higher BP,[16,17,19] lower forearm vascular resistance[17,19] and a synergistic increase in forearm blood flow[17,19] during the task. These studies do not fully clarify mechanisms underlying caffeine's effects on BP regulation, but they do confirm the importance of studying caffeine and behavioral interrelations.

An initial study in our laboratory[20] examined the effects of caffeine (3.3 mg/kg, equivalent to 2 to 3 cups of coffee) compared with placebo during controlled resting conditions in 15 healthy young men (ages 20 to 35). We observed that at rest caffeine's pressor effect was predominantly due to a progressive enhancement of vascular resistance, rather than cardiac stimulation. Cardiac output was not altered by caffeine; in fact, HR decreased slightly, and no evidence was seen of an increased ejection acceleration to indicate enhanced myocardial contractility.

The current study compares hemodynamic mechanisms underlying caffeine's pressor effect during resting conditions versus during manipulation of behavioral state using a highly demanding reaction-time task. Previous experience indicates that cardiovascular responses to such tasks are characterized by increased HR, stroke volume, ejection acceleration and cardiac output, accompanied by decreased systemic vascular resistance[21,22] with a net increase in systolic and diastolic BP. The task-related pattern of cardiovascular activity is similar to that seen during mild aerobic exercise or during mental effort such as making rapid mental arithmetic calculations.[23] Yet it is elicited while limiting necessary physical activity to small finger movements, thereby minimizing breathing, speaking and movement artifacts.

Methods

Forty-four healthy young men (ages 20 to 36) volunteered for the study with informed consent. No volunteers reported known cardiovascular disease, regular smoking, recreational or prescription drug use or caffeine intolerance. Each participant completed 2 test sessions scheduled at the same time of day. Prior abstinence was required from food and caffeine (12 hours), alcohol (24 hours) and medications (36 hours). Grapefruit juice (6 ounces) alone for the placebo or with 3.3 mg/kg caffeine (equivalent to 2 to 3 cups of coffee) was given according to a double-blind, within-subject crossover design.

HR and BP were measured by an automated Critikon/Dynamap oscillometric monitor. Measurements of left ventricular function were obtained noninvasively using a Surcom 304B impedance cardiograph and companion 7000 microcomputer. The technique and data documenting its reliability have been described elsewhere.[20]

Procedure: Upon entering the laboratory each participant completed a questionnaire to confirm current good health and compliance with dietary restrictions. Then a predose of placebo or caffeine was given with the instructions to drink it as rapidly as possible. Surface electrocardiographic and aluminum strip impedance electrodes were attached to the skin. A phonocardiographic microphone, held in place by an elastic strap, was placed 2 to 3 cm above the left nipple and just left of midline. A heparinized Teflon® intravenous catheter was inserted in a left forearm vein to permit periodic blood sampling with minimum disruption. A BP cuff was placed on the upper left arm. The complete instrumentation process required 20 minutes and overlapped the first half of the postdrug absorption period.

Participants were then seated in a semirecumbant position and asked to remain awake while quietly reading general interest news or science publications for an additional 20-minute postdrug rest period. Then participants were instructed to begin a 15-minute behavioral task, which involved watching a small red signal light illuminated for 60 trials at unpredictable intervals. Successful performance required maintaining intense concentration and rapid responding by depressing a telegraph key as soon as the signal light appeared. Bonuses of 50 cents were earned for each extremely fast response (<270 ms). Immediate feedback was given for successful responses. A resting recovery period of 20 minutes followed the task.

Dependent variables and sampling procedures: HR and BP were sampled at 2-minute intervals, and their averages were calculated for the following experimental periods: (1) *postdrug resting baseline* was a 10-minute period begun 30 minutes after drug administration; (2) *behavioral task* was a 15-minute period of continuous task performance; and (3) *recovery baseline* was a 5-minute period begun 15 minutes after task completion. Impedance-derived measurements were obtained on 2 to 3 cardiac cycles per minute and then averaged for each of these experimental periods. Immediately after the cardiovascular measurements

were made for baseline and task periods, residual heparin was removed from the intravaneous catheter and 15 cc of blood was drawn for later determination of plasma caffeine, cortisol and norepinephrine concentrations. The catheter was reheparinized to prevent clotting during subsequent periods.

Systemic vascular resistance and 2 indexes of cardiac work were calculated according to standard formulas. Systemic vascular resistance = (mean BP/cardiac output) × 80. Minute work index = (mean BP/cardiac output). Myocardial oxygen demand estimated from the rate-pressure product = (HR × systolic BP).

Assays: Immediately after each blood sample was drawn the plasma was separated and stored on ice until the end of the session. The plasma was then transferred to storage at −70°C until batched assays were performed. Blood for norepinephrine determinations was collected in 15-cc vacutainer tubes preinjected with glutathione, and plasma concentrations were quantified using radioenzymatic assay (UpJohn Cat-A-Kit). Plasma cortisol concentrations were quantified by radioimmunoassay (Travenol Laboratories' Gamma-Coat). Caffeine was isolated from plasma using acetonitrile precipitation and quantified by high-pressure liquid chromatography.[24]

TABLE I Subject Characteristics

	Mean	Range	(± SEM)
Age (yrs)	23	21–36	0.4
Height (in)	71	66–77	0.3
Weight (lb)	166	115–210	2.6
Percent ideal weight	106	85–125	0.1
Caffeine use (mg/day)	424	30–1,937	63

Caffeine use was based on structured recall for coffee, tea, chocolate and medicinal sources; median use was 316 mg daily.
SEM = standard error of the mean.

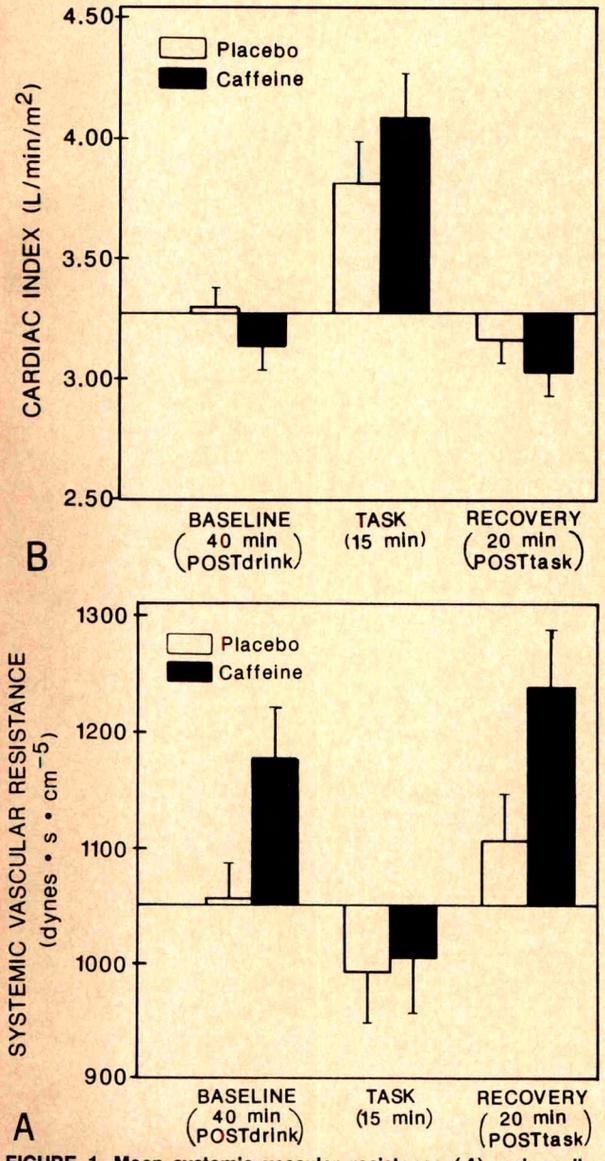

FIGURE 1. Mean systemic vascular resistance (*A*) and cardiac index (*B*), at 40-minute postdrink baseline during 15-minute behavioral task and at 20-minute post-task recovery. Cardiac index is defined as cardiac output divided by body surface area.

Results

The ages, height, weight and self-reported caffeine use for the 41 men included in the final study population are summarized in Table I. Data were omitted for 2 men due to difficulty in obtaining valid impedance measurements, and for another volunteer whose plasma caffeine concentrations were unacceptably elevated on the placebo day (>2.5 μg/ml), indicating either a dosing error or caffeine consumption during the required abstinence period.

Effectiveness of the double-blind drug administration was confirmed by asking the men immediately after each session to predict whether they had received caffeine. Neither correct predictions of caf-

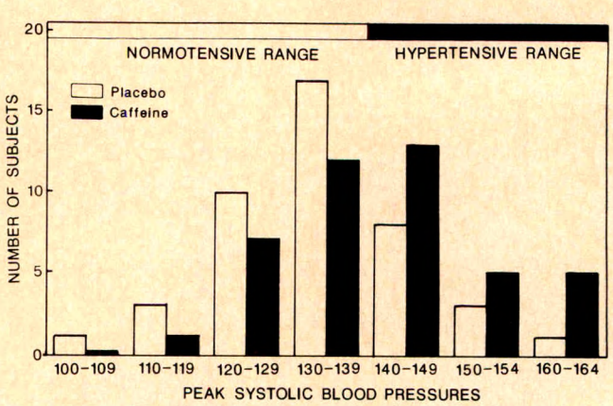

FIGURE 2. Peak systolic blood pressures obtained during the behavioral task on placebo compared with caffeine days. Normotensive versus hypertensive ranges are typically defined using casual measurements obtained after 5 minutes of rest in a seated posture. The peak pressures obtained during the behavioral task could have clinical significance, if they are representative of sustained responses during naturally occurring stressors.

TABLE II Cardiovascular and Endocrine Responses to Caffeine Versus Placebo During Rest and a Behavioral Challenge Task

	Placebo		Caffeine		F Values		
Variables	Rest	Task	Rest	Task	Caffeine (at rest)	Task	CXT
Heart rate (beats/min)	60 ± 1	71 ± 2	58 ± 1	72 ± 2	7.3*	58.7†	4.8*
Systolic BP (mm Hg)	119 ± 1	127 ± 2	123 ± 2	133 ± 2	13.9†	56.7†	2.1
Diastolic BP (mm Hg)	65 ± 1	68 ± 1	70 ± 1	73 ± 1	46.1†	14.9†	0.6
Stroke volume (ml)	106 ± 3	105 ± 4	105 ± 4	109 ± 4	0.2	2.6	8.0†
Ejection acceleration (ohms/ms^2)	14 ± 1	17 ± 1	13 ± 1	18 ± 1	14.9†	37.7†	15.0†
Cardiac output (index) (liter/min/m^2)	3.3 ± 0.1	3.8 ± 0.2	3.1 ± 0.1	4.1 ± 0.2	3.1	49.2†	12.9†
Vascular resistance (dynes·s/cm^5)	1,050 ± 35	991 ± 42	1,176 ± 45	1,003 ± 46	21.1†	49.0†	22.5†
Minute work index	68 ± 2	85 ± 4	69 ± 2	97 ± 4	0.8	56.2†	10.0†
Rate-product pressure	7,156 ± 170	8,983 ± 306	7,147 ± 181	9,652 ± 402	0.0	60.0†	5.0*
Caffeine (μg/ml)	0.13 ± 0.04	0.16 ± 0.05	4.54 ± 0.27	4.62 ± 0.25	320.4†	—	—
Norepinephrine (pg/ml)	250 ± 17	273 ± 14	290 ± 17	317 ± 16	8.9†	5.4*	0.1
Cortisol (μg/100 ml)	12.5 ± 0.7	13.0 ± 0.6	11.6 ± 0.8	14.0 ± 0.7	1.2	15.9†	9.2†

* $p < 0.05$; † $p < 0.01$.
Data are mean ± standard error of the mean.

feine drinks (59%) nor of drug-order conditions (49%) were better than chance.

There were no effects of drug order (placebo-caffeine vs caffeine-placebo) or of session day (day 1 vs day 2) on the initial postdrug resting baseline values summarized in Table II. One-way analyses of variance comparing placebo with caffeine days showed that the present results replicate our previous findings. Under resting conditions, caffeine increased systolic BP and diastolic BP by elevating vascular resistance rather than by enhancing cardiac output. Additionally, caffeine increased resting plasma norepinephrine levels.

The effects of caffeine and the task (Table II) were examined using 1-way analyses of variance with repeated measures for 2 drug conditions (placebo vs caffeine) and 2 experimental periods (postdrug baseline vs task). Task-related cardiovascular responses on either day were characterized by increased HR, stroke volume, ejection acceleration and cardiac output accompanied by decreased vascular resistance. This hemodynamic response pattern increased systolic BP via enhanced cardiac stimulation (Figure 1), a pressor mechanism opposite to that seen with caffeine at rest. Performance of the task was also associated with elevated levels of plasma norepinephrine.

Caffeine's effects during the behavioral task were qualitatively different from those observed at rest (Table II). During the task caffeine no longer elevated vascular resistance. Instead caffeine synergistically increased task-related increments in cardiac output (Figure 1), apparently through heart rate, ejection acceleration and stroke volume. The combination of caffeine and the task increased the number of men with *peak* blood pressures reaching hypertensive levels (Figure 2). Further, caffeine increased cardiac work as estimated by 2 commonly used indexes: the minute work index and the rate × pressure product estimate of myocardial oxygen demand. The caffeine-induced increase in norepinephrine concentrations seen at rest during the postdrug baseline was additive with the task-related elevation. While caffeine did not affect cortisol concentrations at rest, it potentiated the task-related increase in plasma cortisol levels. Caffeine did not significantly improve reaction-time performance; the average number of rewards earned was 18 on the placebo day and 19 on the caffeine day ($p > 0.50$).

Most cardiovascular variables returned rapidly to near postdrug resting levels after the task. Because caffeine's effects during the initial rest period were opposite those seen during the task it seemed possible that either pattern (enhanced vascular resistance or cardiac stimulation accompanied by decreased vascular resistance) might dominate during the after-task recovery baseline, or that their opposing action might obviate any persistent effect of caffeine after the task was terminated. We found that caffeine's pressor effect persisted during recovery, predominantly due to rapid reinstatement of an elevated vascular resistance (Figure 1).

Discussion

These findings help clarify disagreements concerning the mechanisms underlying caffeine's pressor effect. It appears that caffeine's pressor effect may be produced either by increased vascular resistance or cardiac output. At least in healthy young men, the elevated vascular resistance appears to predominate during resting conditions, while potentiation of cardiac stimulation predominates during periods of behavioral arousal. The *resting* elevation in vascular resistance is consistent with the current view that many of caffeine's effects at concentrations achieved by dietary use are related to adenosine antagonism.[13] Whether caffeine's potentiation of β-adrenergically mediated responses *to a behavioral challenge* involve additional central or peripheral enhancement of sympathetic ac-

tivity merits further examination. We found that both caffeine and the task increased plasma norepinephrine levels, but the relation is additive rather than interactive. No data were available for plasma epinephrine.

Other investigators[17,19] have suggested that caffeine might actively enhance vasodilation during mental stress based on the observation that caffeine synergistically increased forearm blood flow and decreased forearm vascular resistance during performance of mental arithmetic. However, methodologic difficulties with the forearm blood flow measurements prevented adequate calibration and also limited the extent to which the vasodilation hypothesis could be supported. In the current study we also observed that caffeine synergistically decreased systemic vascular resistance during the behavioral task compared with the pretask baseline. However, the average level of systemic vascular resistance during the task was equivalent on both caffeine and placebo days. Thus, it appears that caffeine did not produce a net enhancement of systemic vasodilation. Instead the previous caffeine-induced elevation in vascular resistance seen at rest was eliminated during the task.

The health consequences of caffeine use may then partially depend on complex interactions with the extent and duration of behavioral/emotional stressors. Caffeine consumption may be increased during periods of chronic stress, such as during heightened occupational demand.[25] Our findings suggest that caffeine may potentially contribute to pressor responses extending into hypertensive ranges and may synergistically enhance cardiac workload during naturally occurring stressors. Particularly in persons with or at risk for the development of cardiovascular diseases, both caffeine's vasoconstrictive effects and its enhancement of stress-related cardiac stimulation may adversely affect the disease processes. Possible circulatory benefits from caffeine's enhancement of cardiac stimulation appear to be limited, because we were unable to find evidence supporting earlier speculation that such effects were accompanied by net vasodilation.

Further, when designing and interpreting future studies it should be recognized that caffeine's effects may be altered by psychologic or behavioral factors, particularly when invasive or obtrusive procedures are used. Earlier studies that reported that caffeine increased cardiac output relied on measurements made during rebreathing procedures or during cardiac catheterization.[2,3,5,26] It seems possible that either the discomfort and disruption of respiratory patterns frequently associated with rebreathing techniques or the anxiety associated with the invasiveness, risks and diagnostic implications of cardiac catheterization may have produced interactions like those seen between caffeine and our behavioral task.

A more general methodologic precaution concerns the effect of dietary caffeine intake on diagnostic tests or research protocols. Interpretation of acute stress studies or ambulatory monitoring data may be affected by interactions between caffeine and the primary conditions being investigated. Such studies may be improved either by restricting caffeine intake or by documenting the amount consumed to permit the use of statistical control procedures.

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Lisinopril Versus Lisinopril plus Hydrochlorothiazide in Essential Hypertension

JAWAHAR MEHTA, MD, LARRY M. LOPEZ, PharmD, and ALFRED D. THORMAN, PA-C

The efficacy of a new angiotensin converting enzyme inhibitor, lisinopril, used alone (group A) was compared with lisinopril plus hydrochlorothiazide (group B) in 26 patients with essential hypertension. Therapy with both regimens was equally effective in lowering blood pressure compared to placebo. Mean antihypertensive dose of lisinopril was lower when given in combination with hydrochlorothiazide than when given alone (48 ± 6 vs 68 ± 12 mg daily). Plasma renin activity increased in both groups of patients, but more in group B ($p < 0.05$). Plasma aldosterone concentrations and serum uric acid levels were also higher in the group receiving lisinopril plus hydrochlorothiazide ($p < 0.05$). Serum potassium concentrations were unaffected in either group. The incidence of side effects was similar in groups A and B (44% and 38%, respectively). This study suggests that lisinopril alone or in combination with hydrochlorothiazide effectively lowers blood pressure in patients with essential hypertension without any major side effects.

(Am J Cardiol 1988;61:803–806)

Initial pharmacotherapy for most patients with essential hypertension consists of β-adrenergic blockers or diuretics.[1–3] Because these agents may have unacceptable side effects, initial therapy with other agents, such as calcium antagonists,[4] centrally acting α_2-adrenoceptor agonists[5] and angiotensin converting enzyme (ACE) inhibitors[5,6] has been recently advocated. The ACE inhibitors exert minimal side effects[6,7] and, therefore, are appropriate in a variety of patients. However, ACE inhibitors currently marketed in the U.S. may occasionally cause proteinuria and bone marrow depression.[8,9] Recently, a new ACE inhibitor, lisinopril, was developed.[10] It is a lysine analog of enalaprilat, which itself is the active metabolite of enalapril, an ACE-inhibitor prodrug. In previous studies, lisinopril has been shown to be as potent as enalapril, but with longer duration of action. Its hemodynamic effects appear at 2 to 4 hours after administration and persist for more than 24 hours.[10] This study examines the efficacy of lisinopril alone and in combination with hydrochlorothiazide in patients with essential hypertension.

From the Departments of Medicine, Pharmacy Practice and Ambulatory Services of the University of Florida Colleges of Medicine and Pharmacy, and the Veterans Administration Medical Center, Gainesville, Florida. This study was supported in part by the Research Service of the Veterans Administration, Washington, D.C., and Merck, Sharp and Dohme Laboratories, West Point, Pennsylvania. Manuscript received October 16, 1987; revised manuscript received December 7, 1987, and accepted December 8.

Address for reprints: Jawahar Mehta, MD, Division of Cardiology, Veterans Administration Medical Center (111D), Gainesville, Florida 32602.

Methods

Patient selection: Patients recruited for this trial were men over 18 years of age with mild to moderate essential hypertension defined as untreated diastolic blood pressure (BP) of 90 to 114 mm Hg. Patients were excluded if they had a history of a cerebrovascular accident, hypertensive encephalopathy or myocardial infarction within the past year. Patients with a history of drug or ethanol abuse or hypersensitivity to either thiazide diuretics or ACE inhibitors were likewise excluded. Other exclusion criteria included significant renal, hepatic or hematologic disorders and the presence of grade 3 or 4 hypertensive retinopathy.

Protocol: Each qualifying patient was entered into the first of 3 study phases after gradual discontinuation of all existing antihypertensive medications. The first phase involved single-blind administration of placebo for 4 weeks. Every patient was instructed to take medication once daily upon arising in the morning. BP and heart rate were determined during weekly clinic visits before administration of medication. Complete physical and laboratory examinations were performed at the end of withdrawal of antihypertensive therapy and the 4-week placebo period. Each patient with a sitting diastolic BP of 90 to 114 mg Hg was randomized to

TABLE I Patient Characteristics

	Lisinopril Alone	Lisinopril + Hydrochlorothiazde
No.	13	9
Age* (yrs)	57 ± 1	53 ± 4
Weight (pounds)	202 ± 5	205 ± 12
Duration of hypertension (yrs)	11 ± 4	5 ± 1
Seated blood pressure (mm Hg)	144 ± 4/97 ± 2	148 ± 4/96 ± 1
Erect blood pressure (mm Hg)	148 ± 5/103 ± 2	151 ± 5/99 ± 1

* Data are expressed as mean ± standard error of the mean.

TABLE II Adverse Effects of Lisinopril Alone and with Hydrochlorothiazide

Lisinopril Alone (Group A)	Lisinopril + Hydrochlorothiazide (Group B)
Disorientation (1)	Rash (1)
Nocturia (1)	Impotence (1)
Dry throat (1)	Increased uric acid (1)
Frequency (1)	Postural dizziness (1)
Postural dizziness (1)	Lightheadedness (1)
Reduced exercise tolerance (1)	
Increased alkaline phosphatase (1)	

Number in parentheses represents number of patients complaining of adverse effect.

active therapy if the difference between the last 2 diastolic BPs was ≤10 mm Hg.

Randomization to active therapy marked the beginning of the second phase. Patients were randomly assigned to lisinopril alone (group A) or lisinopril plus hydrochlorothiazide (group B). Double-blind medication was administered once daily and dose was titrated upward every 4 weeks to a sitting diastolic BP of <90 mm Hg and a decrease in sitting diastolic BP ≥10 mm Hg. The daily dose of lisinopril in group A was begun at 20 mg and increased to 40 mg and then to 80 mg, if needed. The daily doses of lisinopril and hydrochlorothiazide in group B were begun at 20 and 12.5 mg, respectively, increased to 40 and 25 mg, and then to a maximum of 80 and 50 mg, respectively, as needed. At the end of this phase, if BP goal was not achieved, the patient was removed from the study and returned to previous antihypertensive therapy. If BP goal was realized, however, the patient then entered the third phase of the study, which was a treatment period lasting 12 weeks. The dose of double-blind medication associated with adequate BP reduction in the second phase was continued throughout this phase. As in the previous phase, BP and heart rate were evaluated biweekly in sitting and erect positions. Complete physical and laboratory examinations were performed every 4 weeks, and patients were interviewed during each clinic visit concerning occurrence of side effects. During all phases, compliance was assessed with tablet counts and patients were instructed to continue their usual diet. Medications know to affect BP were not allowed, and other medications taken during this study were tabulated.

Laboratory tests: Laboratory tests included evaluation of hematologic, renal and hepatic functions. Plasma renin activity, plasma aldosterone levels, serum uric acid and potassium levels were also measured. All of these analyses were performed by Smith-Kline/Bioscience Laboratories. Blood was collected from all patients at the end of placebo, titration and treatment phases in supine position after at least 15 minutes of rest between 8 and 9 A.M., before the drug intake. No attempt was made to regulate patients' dietary habits or salt intake, as each patient served as his own control.

Statistical analysis: The study code was unblinded at the end of the treatment phase. Heart rate and BP data were averaged for all groups. Data are presented as mean ± standard error. The effects of the 2 forms of therapy on BP were determined by 1-way repeated measures analysis of variance and the Student *t* test for paired data. Frequency data were analyzed using Fischer's exact test. Laboratory data were evaluated for changes in plasma renin activity, plasma aldosterone concentrations, serum uric acid and potassium concentrations associated with the use of lisinopril alone or in combination with hydrochlorothiazide.

Results

Out of 29 patients initially screened for entry into this trial, 26 qualified. Of these 26, 3 were unable to receive double-blind medication due to adverse events encountered during placebo phase (one had a nonfatal myocardial infarction, one had ventricular arrhythmias and the third developed a rash). One patient was removed from the trial at the end of the titration phase when his BP failed to decrease sufficiently. Table I summarizes the clinical and demographic characteristics of the remaining 22 patients who completed all phases of the study. The 2 groups were comparable, except that group A patients had hypertension of longer duration.

Effects of lisinopril alone and in combination with hydrochlorothiazide on BP and heart rate are presented in Figure 1. BP in both supine and erect positions was significantly reduced with minimal effects on heart rate. Comparisons of these changes failed to achieve statistical significance between the groups even though the daily dose of lisinopril in group B was somewhat less than that in group A (48 ± 6 vs 68 ± 12 mg, $p = 0.15$).

The effects of lisinopril administration alone and in combination with hydrochlorothiazide on selected metabolic parameters (plasma renin activity, plasma aldosterone concentrations, serum potassium and uric acid concentrations) are depicted in Figure 2. Plasma renin activity increased significantly in both groups of patients, but the magnitude of this increase was more pronounced ($p < 0.05$) in group B patients. Aldosterone concentrations were lowered in patients receiving lisinopril alone ($p < 0.05$) but were unchanged in patients receiving both medications. Serum potassium concentrations were unaffected in both groups of patients. When hydrochlorothiazide was combined with lisinopril, uric acid concentration increased signifi-

cantly ($p < 0.01$), but not when lisinopril was given alone.

All adverse effects reported by patients during double-blind titration and treatment phases are listed in Table II. Frequency of these adverse effects did not differ between the study groups, nor did proportions of patients experiencing them (44% group A; 38% group B; difference not significant). Postural dizziness occurred in both groups and in both instances was not accompanied by clinically important changes in BP. Lisinopril did not cause an adverse effect on proteinuria, renal function or other laboratory parameters. It is noteworthy that a small but significant reduction in hematocrit was observed in both groups (46% to 43%, group A; 45% to 42%, group B; $p < 0.01$ for both). All adverse effects encountered were minor in nature and none required discontinuation of therapy in any patient.

Discussion

This study demonstrates that lisinopril alone and in combination with hydrochlorothiazide is effective as initial pharmacotherapy in the management of patients with essential hypertension. Although both therapeutic regimens were equally effective, the dose of lisinopril required to decrease BP was lower when used in combination with hydrochlorothiazide compared with lisinopril alone. It is noteworthy that both regimens caused no significant tachycardia, either in the sitting or standing position.

Comparable BP responses to combination therapy with a low dose of lisinopril plus hydrochlorothiazide and lisinopril alone may be expected, because the 2 drugs act via different mechanisms and may act synergistically. Whereas hydrochlorothiazide is a diuretic and stimulates the renin-angiotensin-aldosterone axis secondary to reduction of plasma volume, lisinopril inhibits the same axis by blocking conversion of angiotensin I to angiotensin II. A cumulative antihypertensive response became apparent when small doses of both drugs were administered concomitantly. Similar cumulative effects between diuretics and other ACE inhibitors have been described previously.[11] Sodium loss associated with thiazide diuretics is increased when the diuretics are combined with the ACE inhibitor enalapril.[11] The resultant loss of fluid volume potentiates the hypotensive effect of the ACE inhibitor.

Lisinopril alone or in combination with hydrochlorothiazide lowered BP quickly (≤4 weeks) and that reduction in BP after titration of dose was maintained throughout the remainder of the study. In spite of rapid and sustained reduction in BP, we did not observe any objective incidence of orthostasis. This was perhaps related to the relatively slow onset of the action of lisinopril with a peak action at 2 to 4 hours.[10] No patient was withdrawn because of the development of side effects, although side effects were frequent and similar in both groups (44% of patients in the lisinopril group, and 38% of patients in the lisinopril plus hydrochlorothiazide group). The somewhat lower frequency of side effects in the latter group may be explained by the use of small amounts of 2 different drugs.

The effects of lisinopril alone or its combination on plasma renin activity, plasma aldosterone levels and serum potassium levels are interesting, although not unexpected (Figure 2). Plasma renin activity increased in both groups, although to a greater extent in the lisinopril plus hydrochlorothiazide group, perhaps because of volume depletion. Plasma renin activity increased during the titration phase and continued to increase into the treatment phase. Plasma aldosterone concentrations were higher in the combination treatment group than in the lisinopril alone group, again a reflection of the varied mechanisms of action of the 2 agents. Serum potassium levels were unchanged in both groups. Similar responses have been observed before.[12] Diuretic-induced hypokalemia occurs as a result of excess delivery of sodium to the distal renal tubule and secondary hyperaldosteronism. Effects of both the reduction in circulating volume and secondary hyperaldosteronism are blunted by the concurrent administration of ACE inhibitor.[11] Serum uric acid concentrations, however, were increased in the group B patients, related most likely to the well known,

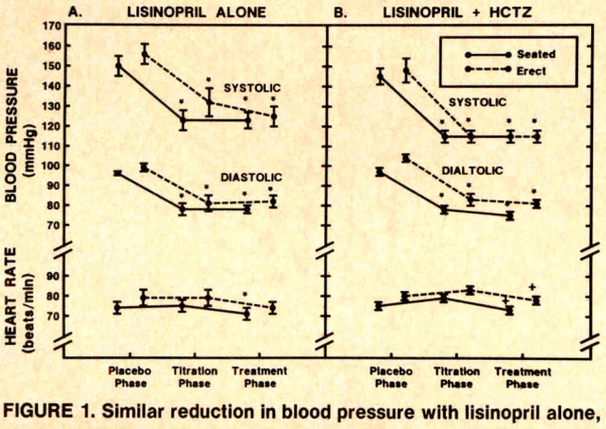

FIGURE 1. Similar reduction in blood pressure with lisinopril alone, *A*, or lisinopril plus hydrochlorothiazide (HCTZ), *B*. There was no evidence of significant orthostasis. Heart rate was minimally changed by both regimens.

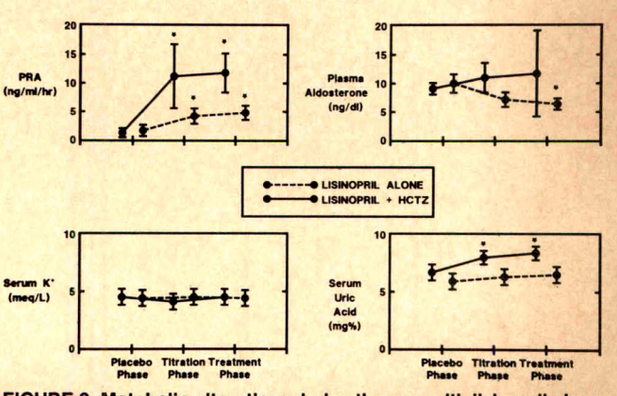

FIGURE 2. Metabolic alterations during therapy with lisinopril alone or combination of lisinopril and hydrochlorothiazide (HCTZ). (See text.) PRA = plasma renin activity.

antiuricosuric effect of thiazide diuretics. Of note is the slight decrease in hematocrit in patients receiving lisinopril alone and in combination with hydrochlorothiazide, but this reduction did not appear to be of clinical significance. Whether this abnormality would be clinically significant when these drugs are used in larger numbers of patients for prolonged periods is not known.

In summary, this study demonstrates a similar efficacy of lisinopril plus hydrochlorothiazide and lisinopril alone. When the combination regimen is used, the dosage of each agent is quite low. In this short-term trial, the incidence of side effects was small and acceptable.

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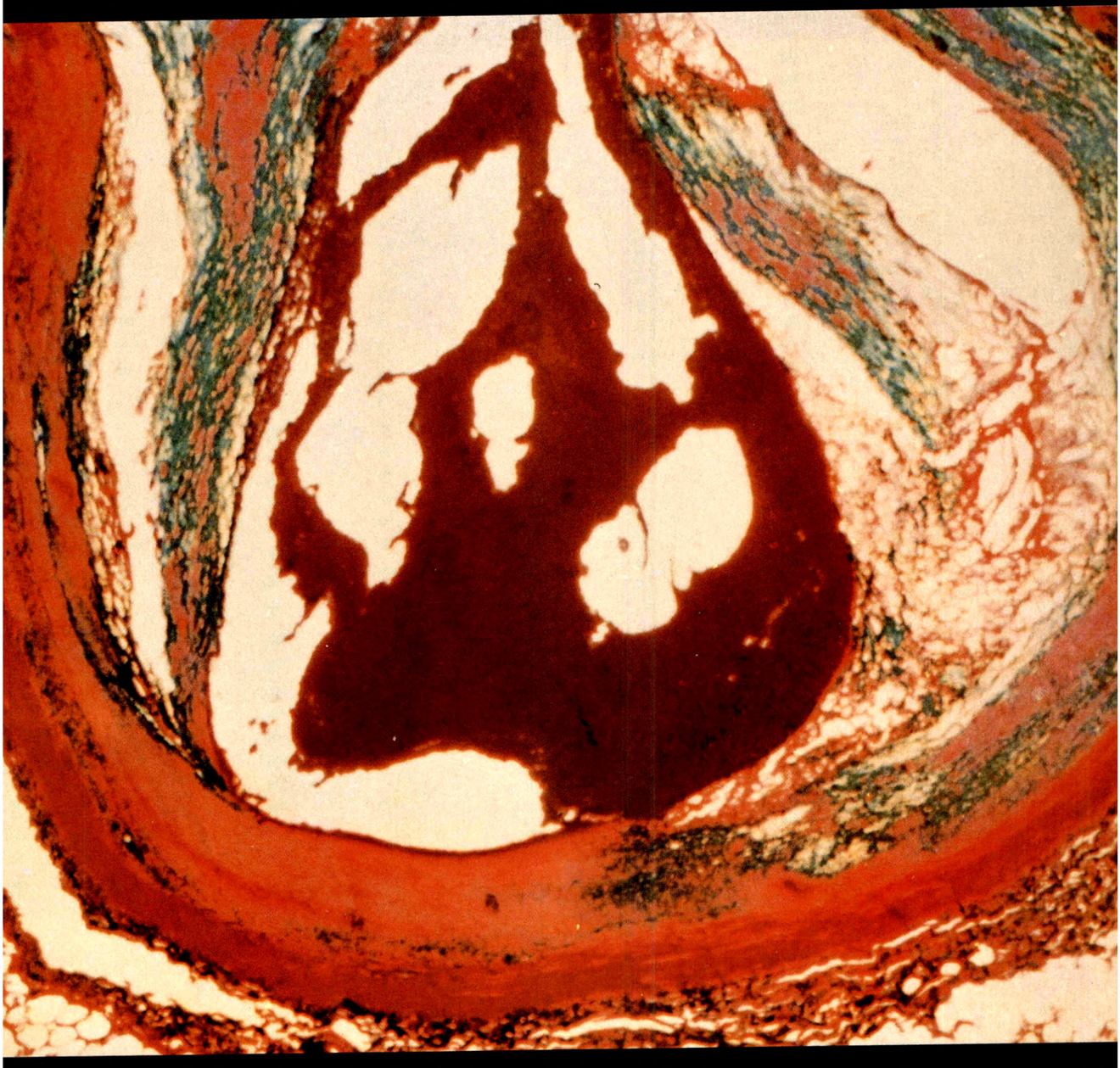

Cross section of a cardiac artery showing atheromatous plaque and occluding thrombus.

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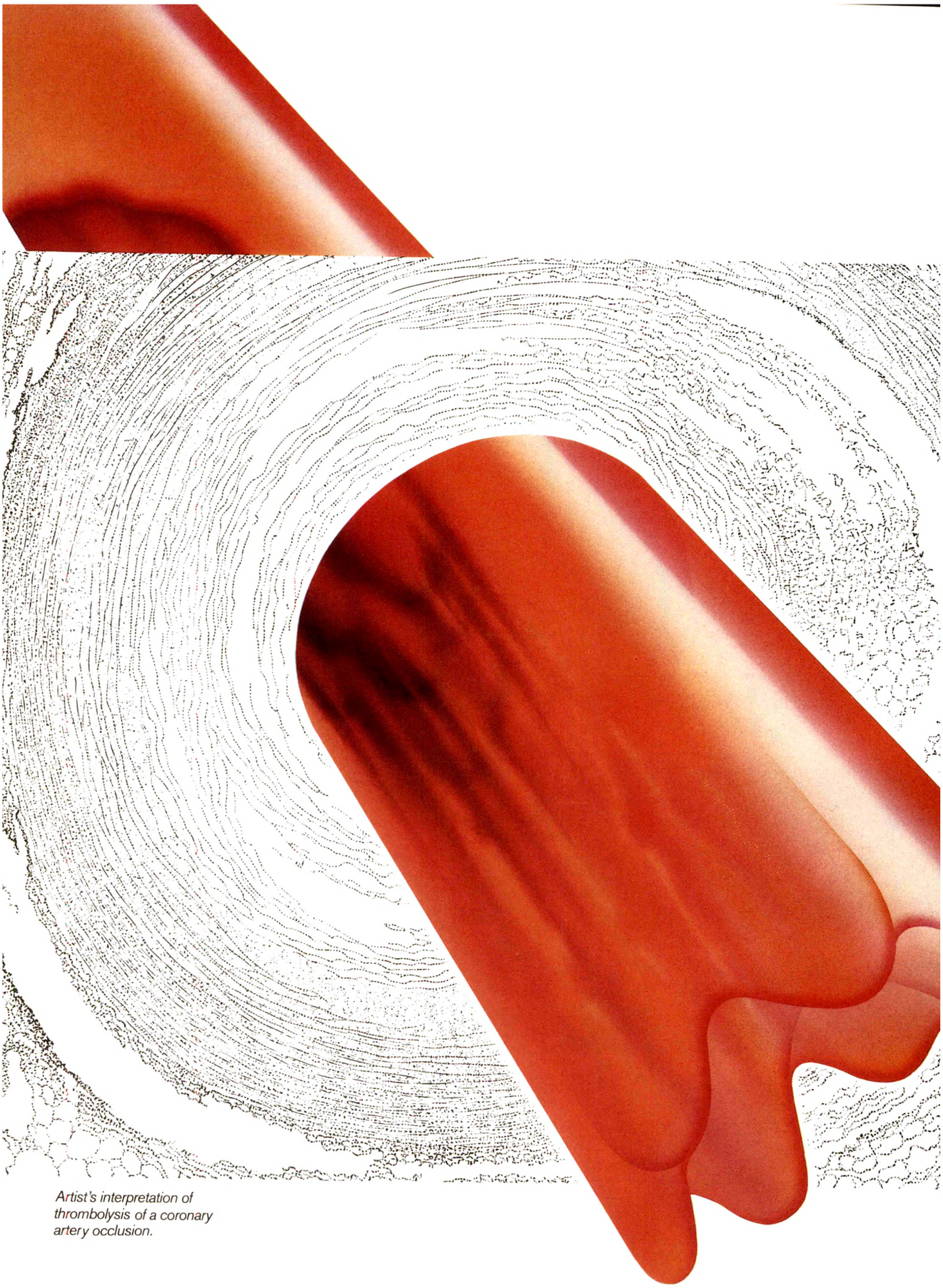

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- Coronary artery reperfusion shown by earlier peak of myocardial creatine kinase
- Significant increase in left ventricular ejection fraction and significant reduction in end-systolic volume confirmed by left ventricular angiography
- In this study, the most serious adverse effect was manageable hypotension

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- Decreases red blood cell aggregation, and plasma and blood viscosity[3-5]
- Reduces blood pressure and total peripheral resistance with corresponding reduction in cardiac afterload for reduced myocardial oxygen demand[6-8]

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—*Risk of bleeding:* From pooled data of studies of 8,369 patients, the overall incidence of major bleeding was 1.2%. Nonetheless, physicians should be alert to untoward bleeding events. (Consult Warnings section of Streptase full prescribing information.)

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Bleeding, allergy and fever are the most frequent side effects seen with streptokinase; during treatment of myocardial infarction, hypotension and arrhythmias have been reported. Please see Warnings section of prescribing information before using Streptase®.

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STREPTASE®
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Brief Summary
Consult full prescribing information before using.

INDICATIONS AND USAGE
Acute Evolving Transmural Myocardial Infarction
Streptase®, Streptokinase, is indicated for use in the management of acute myocardial infarction in adults, for the lysis of intracoronary thrombi, for the improvement of ventricular function, and reduction of mortality when administered by either the intravenous or intracoronary route. Earlier administration of Streptokinase is correlated with greater clinical benefit. See CLINICAL PHARMACOLOGY section of full prescribing information.

CONTRAINDICATIONS
Because thrombolytic therapy increases the risk of bleeding, Streptase®, Streptokinase, is contraindicated in the following situations:
- —Active internal bleeding
- —Recent (within 2 months) cerebrovascular accident, intracranial or intraspinal surgery (see WARNINGS)
- —Intracranial neoplasm
- —Severe uncontrolled hypertension.

Streptokinase should not be administered to patients having experienced severe allergic reaction to the product.

WARNINGS
Bleeding
Streptase®, Streptokinase, will cause lysis of hemostatic fibrin deposits such as those occurring at sites of needle punctures, and bleeding may occur from such sites. In order to minimize the risk of bleeding during treatment with Streptokinase, venipunctures and physical handling of the patient should be performed carefully and as infrequently as possible, and intramuscular injections must be avoided.
Should arterial puncture be necessary during intravenous therapy, upper extremity vessels are preferable. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.
In the following conditions the risks of therapy may be increased and should be weighed against the anticipated benefits.
- —Recent (within 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels
- —Recent (within 10 days) serious gastrointestinal bleeding
- —Recent (within 10 days) trauma including cardiopulmonary resuscitation
- —Hypertension: systolic BP ≥ 180 mm Hg and/or diastolic BP ≥ 110 mm Hg
- —High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- —Subacute bacterial endocarditis
- —Hemostatic defects including those secondary to severe hepatic or renal disease
- —Pregnancy
- —Cerebrovascular disease
- —Diabetic hemorrhagic retinopathy
- —Septic thrombophlebitis or occluded AV cannula at seriously infected site
- —Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Should serious spontaneous bleeding (not controllable by local pressure) occur, the infusion of Streptase®, Streptokinase, should be terminated immediately and treatment instituted as described under ADVERSE REACTIONS.

Arrhythmias
Rapid lysis of coronary thrombi has been shown to cause reperfusion atrial or ventricular dysrhythmias requiring immediate treatment. Careful monitoring for arrhythmia is recommended during and immediately following administration of Streptase®, Streptokinase, for acute myocardial infarction.

Hypotension
Hypotension, sometimes severe, not secondary to bleeding or anaphylaxis has been observed during intravenous Streptase®, Streptokinase, infusion in 1% to 10% of patients. Patients should be monitored closely and, should symptomatic or alarming hypotension occur, appropriate treatment should be administered. This treatment may include a decrease in the intravenous Streptokinase infusion rate. Smaller hypotensive effects are common and have not required treatment.

Other
Non-cardiogenic pulmonary edema has been reported rarely in patients treated with Streptase®, Streptokinase. The risk of this appears greatest in patients who have large myocardial infarctions and are undergoing thrombolytic therapy by the intracoronary route.
Rarely, polyneuropathy has been temporally related to the use of Streptase®, Streptokinase.
Should pulmonary embolism or recurrent pulmonary embolism occur during Streptase®, Streptokinase, therapy, the originally planned course of treatment should be completed in an attempt to lyse the embolus. While pulmonary embolism may occasionally occur during Streptokinase treatment, the incidence is no greater than when patients are treated with heparin alone.

PRECAUTIONS
General
Because of the increased likelihood of resistance, due to antistreptokinase antibody, Streptase®, Streptokinase, may not be effective if administered between five days and six months of prior Streptokinase administration or streptococcal infections, such as streptococcal pharyngitis, acute rheumatic fever, or acute glomerulonephritis secondary to a streptococcal infection.

Laboratory Tests
Intravenous or Intracoronary Infusion for Myocardial Infarction
Intravenous administration of Streptase®, Streptokinase, will cause marked decreases in plasminogen and fibrinogen and increases in thrombin time (TT), activated partial thromboplastin time (APTT), and prothrombin time (PT). These changes may also occur in some patients with intracoronary administration of Streptokinase.
Intravenous Infusion for Other Indications. Before commencing thrombolytic therapy, it is desirable to obtain an activated partial thromboplastin time (APTT), a prothrombin time (PT), a thrombin time (TT), fibrinogen levels, and a hematocrit and platelet count. If heparin has been given, it should be discontinued and the TT or APTT should be less than twice the normal control value before thrombolytic therapy is started.
During the infusion, decreases in plasminogen and fibrinogen levels and an increase in the level of FDP (the latter two causing a prolongation in the clotting times of coagulation tests) will generally confirm the existence of a lytic state. Therefore, lytic therapy can be confirmed by performing the TT, APTT, PT, or fibrinogen levels approximately 4 hours after initiation of therapy. If heparin is to be (re)instituted following the Streptase®, Streptokinase, infusion, the TT or APTT should be less than twice the normal control value (see manufacturer's prescribing information for proper use of heparin).

Drug Interactions
The interaction of Streptase®, Streptokinase, with other drugs has not been well studied.
Use of Anticoagulants and Antiplatelet Agents. Streptase®, Streptokinase, alone or in combination with antiplatelet agents and anticoagulants, may cause bleeding complications. Therefore, careful monitoring is advised. Concurrent use of antiplatelet agents such as aspirin, dipyridamole, or nonsteroidal antiinflammatory agents is not recommended.
Anticoagulation After Treatment for Myocardial Infarction. The administration of anticoagulant and/or antiplatelet drugs following administration of Streptase®, Streptokinase, appears to increase the risk of bleeding (see ADVERSE REACTIONS). These agents have been used in an attempt to prevent reocclusion of the target vessel. Use of anticoagulants or antiplatelet drugs following administration of Streptokinase has not yet been shown to be of unequivocal clinical benefit. Therefore, the use of anticoagulant and/or antiplatelet regimens should be individualized.
Anticoagulation after IV Treatment for Other Indications. Continuous intravenous infusion of heparin, without a loading dose, has been recommended following termination of Streptase®, Streptokinase, infusion for treatment of pulmonary embolism or deep vein thrombosis to prevent rethrombosis. The effect of Streptokinase on thrombin time (TT) and activated partial thromboplastin time (APTT) will usually diminish within 3 to 4 hours after Streptokinase therapy, and heparin therapy without a loading dose can be initiated when the TT or the APTT is less than twice the normal control value.

Pregnancy
Pregnancy Category C. Animal reproduction studies have not been conducted with Streptase®, Streptokinase. It is also not known whether Streptokinase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Streptokinase should be given to a pregnant woman only if clearly needed.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
The following adverse reactions have been associated with intravenous therapy and may also occur with intracoronary artery infusion:

Bleeding
The incidence of bleeding (major or minor) varied widely from study to study depending on dosage, patient population and concomitant therapy.
Minor bleeding can be anticipated mainly at invaded or disturbed sites. If such bleeding occurs, local measures should be taken to control the bleeding.
Severe internal bleeding involving gastrointestinal, genitourinary, retroperitoneal, or intracerebral sites has occurred and has resulted in fatalities. In three studies in which anticoagulation was optional following intravenous administration of Streptase®, Streptokinase, for acute myocardial infarction, the incidence of major bleeding ranged from 0.3%-6.2%. In 21 studies in which anticoagulation was compulsory, the incidence of major bleeding ranged from 0-16%. The overall incidence of major bleeding with intravenous infusion is 1%-2%.
Major bleed rates are difficult to determine for other dosages and patient populations because of the different dosing and intervals of infusions. The rates reported appear to be within the ranges reported for intravenous administration in acute myocardial infarction.
Should uncontrollable bleeding occur, Streptokinase infusion should be terminated immediately. Slowing the rate of administration of Streptokinase will not help correct bleeding and may make it worse. If necessary, bleeding can be reversed and blood loss effectively managed with appropriate replacement therapy. Although the use of aminocaproic acid (ACA, AMICAR®) in humans as an antidote for Streptokinase has not been documented, it may be considered in an emergency situation.

Allergic Reactions
Anaphylactic and anaphylactoid reactions have been observed rarely in patients treated intravenously with Streptase®, Streptokinase. These ranged in severity from minor breathing difficulty to bronchospasm, periorbital swelling or angioneurotic edema. Other milder allergic effects such as urticaria, itching, flushing, nausea, headache and musculoskeletal pain have also been observed, as have delayed hypersensitivity reactions such as vasculitis and interstitial nephritis. Anaphylactic shock was reported in one study with an incidence rate of 0.1%.
Mild or moderate allergic reactions may be managed with concomitant antihistamine and/or corticosteroid therapy. Severe allergic reactions require immediate discontinuation of Streptase®, Streptokinase, with adrenergic, antihistamine, and/or corticosteroid agents administered intravenously as required.

Fever
Although Streptase®, Streptokinase, is nonpyrogenic in standard animal tests, recent reports in the literature have noted an incidence of fever ranging from 0 to 21% in patients treated intravenously with Streptokinase. Symptomatic treatment is usually sufficient to alleviate discomfort. The use of acetaminophen rather than aspirin is preferable.

DOSAGE AND ADMINISTRATION
Acute Evolving Transmural Myocardial Infarction
Administer Streptokinase as soon as possible after onset of symptoms. The greatest benefit in mortality reduction was observed when Streptase®, Streptokinase, was administered within one hour, statistically significant benefits were observed up to six hours and some benefit was observed up to 12 hours without statistical significance (see CLINICAL PHARMACOLOGY in full prescribing information).

Route	Total Dose	Dosage/Duration
Intravenous infusion	1,500,000 IU	1,500,000 IU within 60 min.

HOW SUPPLIED
Streptase®, Streptokinase, is supplied as a lyophilized white powder in 50 mL infusion bottles (1,500,000 IU) or in 6.5 mL vials with a color-coded label corresponding to the amount of purified Streptokinase in each vial as follows:
green— 250,000 IU
blue — 750,000 IU
red — 1,500,000 IU vials and infusion bottles.
Store unopened vials at controlled room temperature (15°-30°C or 59°-86°F). Unused reconstituted drug should be discarded.

Manufactured by: Behringwerke AG
US License No. 97
Distributed by: Hoechst-Roussel Pharmaceuticals Inc.
Somerville, NJ 08876

Edition 11/87A

Intravenous
Streptase®
(Streptokinase)
Now...for acute MI

Manufactured by:
Behringwerke AG, Marburg, West Germany.

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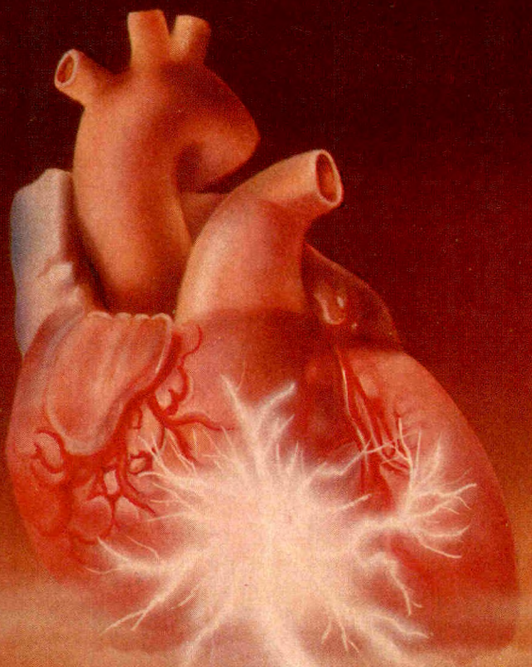


436-8066-A

in Acute MI

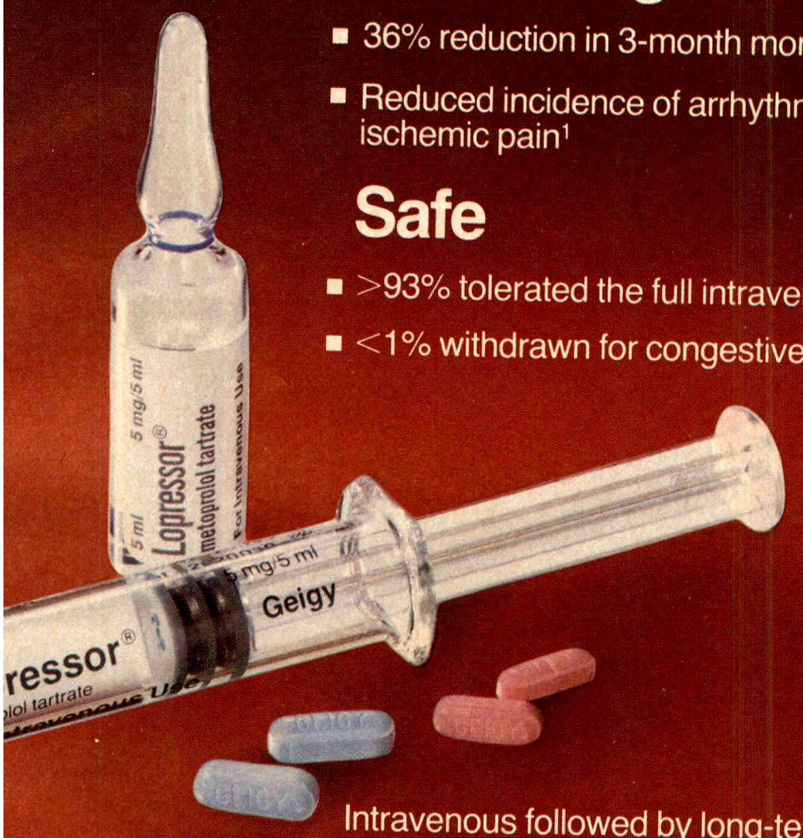
Geigy

Lifesaving

- 36% reduction in 3-month mortality[1]
- Reduced incidence of arrhythmias and ischemic pain[1]

Safe

- >93% tolerated the full intravenous dose[2]
- <1% withdrawn for congestive heart failure[3]



Intravenous followed by long-term oral therapy

Alternatively, oral treatment can begin within 3 to 10 days of the acute event

Lopressor is contraindicated in patients with heart rate <45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥0.24 sec); systolic blood pressure <100 mmHg; or moderate-to-severe cardiac failure.

Please see last page for Brief Summary of Prescribing Information.

The *only* beta blocker indicated in definite or suspected acute myocardial infarction...

Lopressor® in MI

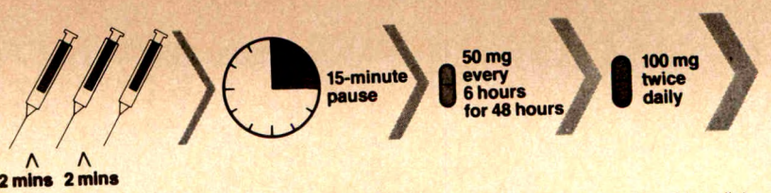
metoprolol tartrate

Prefilled Syringes: 5 mg/5 ml
Ampuls: 5 mg/5 ml
Tablets: 100 mg 50 mg

Changing the Course of Cardiovascular Care

References

1. Hjalmarson A, et al: The Göteborg Metoprolol Trial: Effects on mortality and morbidity in acute myocardial infarction. *Circulation* 1983;67(suppl 1):I-26-I-32.
2. Data on file, Geigy Pharmaceuticals.
3. Herlitz J, et al: Göteborg Metoprolol Trial: Tolerance. *Am J Cardiol* 1984;53:46D-50D.



Lopressor®

metoprolol tartrate USP

Tablets
Ampuls
Prefilled Syringes

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

Hypertension
Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris
Lopressor is indicated in the long-term treatment of angina pectoris.

Myocardial Infarction
Lopressor ampuls, prefilled syringes, and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS

Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS

General
Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypertension and Angina
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.

Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

C86-36 (Rev. 6/

Geigy

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

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436-806

Comparison of the Antihypertensive Effects of Betaxolol to Atenolol

WILLIAM J. MROCZEK, MD, JAMES F. BURRIS, MD, LEO B. HOGAN, MD, DANIEL C. CITRON, MD, ALLAN H. BARKER, MD, and ROBERT H. MCDONALD, MD

A randomized double-blind multicenter study compared a new oral β_1-adrenergic antagonist, betaxolol 10 to 40 mg (n = 71), with atenolol 25 to 100 mg (n = 75). Each drug was administered once daily for 24 weeks in patients with mild to moderate hypertension. Blood pressure (BP) measurements were taken 24 hours after dosing. Each drug produced significant ($p < 0.01$) reductions in mean supine diastolic BP. The mean decrease in supine diastolic BP with betaxolol was significantly greater at weeks 4, 6, 10 and 12 ($p < 0.05$). Throughout the remainder of the trial (weeks 14 to 24), no significant differences in BP reduction were noted between treatment groups. Normotension (supine diastolic BP ≤90 mm Hg) was achieved in 72% of those given betaxolol compared with 52% of those given atenolol ($p < 0.05$). The most common side effects noted were bradycardia, fatigue and headache. The incidence of these and of central nervous system side effects was similar between the betaxolol and atenolol groups. Both agents were well tolerated. At recommended doses, betaxolol once daily may be more effective than atenolol once daily in patients with mild to moderate hypertension.

(Am J Cardiol 1988;61:807–811)

Betaxolol, like atenolol, is cardioselective, lacks partial agonist activity, has little or no membrane stabilizing activity and has no active metabolites.[1–7] Betaxolol has a markedly higher oral bioavailability than atenolol (80 to 89% vs 50 to 60%) and a longer elimination half-life (14 to 22 hours) compared with atenolol (6 to 7 hours).[8–11] Betaxolol has demonstrated effectiveness in reducing blood pressure (BP) when administered once daily in both open and double-blind clinical trials.[12–15] A randomized double-blind multicenter study was conducted to compare the long-term (24 week) efficacy and safety of betaxolol with atenolol taken once daily in patients with mild to moderate essential hypertension.

Methods

Patient population: One hundred forty-six patients with mild to moderate essential hypertension were randomized to receive treatment. Patients with secondary causes of hypertension were excluded from the study. Other reasons for exclusion were severe cardiac arrhythmias, angina pectoris, congestive heart failure, pulmonary disease and insulin-dependent diabetes. Women of child-bearing potential practicing a medically accepted means of contraception were permitted to enter the study.

The protocol was approved by the respective institutional review committee and informed consent was obtained from all patients.

Study design: The study included 4 phases. Phase 1 was an initial 4-week washout period during which all antihypertensive medications were discontinued and patients were given 1 placebo capsule daily at 10 A.M. If the patient's supine diastolic BP was between 95 and 115 mm Hg at the end of the placebo run-in period, he or she was randomized to 1 of 2 treatments and proceeded to the next phase of the trial.

Phase 2 was a 12-week dose-titration period. Patients were seen at 2-week intervals. At 4-week intervals, if supine diastolic BP remained >90 mm Hg, the dosage of betaxolol was increased from 10 to 20 to 40 mg; atenolol was increased from 25 to 50 to 100 mg. Study medications were taken at 10 A.M. The low and high doses in this study were obtained by halving and doubling the usual dose of each agent.

Phase 3 was a 12-week maintenance period during which patients continued to receive their optimal dose

From the Cardiovascular Center of Northern Virginia, Falls Church, Virginia. This study was supported by a grant from Lorex Pharmaceuticals, Skokie, Illinois. Manuscript received July 6, 1987; revised manuscript received and accepted December 9, 1987.

Address for reprints: William Mroczek, MD, Cardiovascular Center of Northern Virginia, 6045 Arlington Boulevard, Falls Church, Virginia 22044.

TABLE I Patient Characteristics at Randomization

	Betaxolol	Atenolol
Pts (n)	71	75
Age (yrs)	49 ± 1	54 ± 1
Range	22–69	31–69
Weight (lbs)	184 ± 5	185 ± 5
Range	107–324	106–304
Sex		
M	45 (63%)	40 (53%)
F	26 (27%)	35 (47%)
Race		
White	64 (90%)	64 (85%)
Black	7 (10%)	11 (15%)
Duration of hypertension (yrs)	8 ± 1	9 ± 1
Baseline supine systolic BP (mm Hg)	147 ± 2	152 ± 2
Baseline supine diastolic BP (mm Hg)	100 ± 1	101 ± 1
Baseline supine heart rate (beats/min)	75 ± 1	74 ± 1
Left ventricular hypertrophy		
Present	15 (21%)	9 (12%)
Absent	56 (79%)	66 (78%)
Optic fundi (KWB-HT)		
O-I	65 (92%)	67 (89%)
II	5 (7%)	8 (11%)
III	1 (1%)	0
Serum creatinine (mg/dl)	1.02 ± 0.02	1.05 ± 0.02

Data are mean ± standard error where appropriate.
BP = blood pressure; KWB-HT = Keith-Wagner-Barker classification limited to hypertensive retinopathy.

TABLE II Reasons for Withdrawal Among the Randomized Patients

	Betaxolol (n = 71)	Atenolol (n = 75)
Side effects	5	3
Intercurrent illness	1	2
Therapeutic failure	2	5
Administrative*	6	5

* Refusal of therapy, lost to follow-up, failure to follow appointment schedule, nonqualifying blood pressure, poor compliance or protocol violation.

of the assigned drug. Phase 4 was a 2-week placebo washout period.

The primary measurements (supine and standing BP and heart rate) were recorded every 2 weeks. At each visit, BP was measured in the morning just before the next dosing after 5 minutes in the supine position and also after 3 minutes in the standing position using a standard mercury sphygmomanometer. An average of 3 recordings was taken and the Korotkoff phase V was used for measuring the diastolic BP. At each visit, patients were queried as to side effects. All patients underwent a full physical examination and a review of their medical histories before entering the trial. Electrocardiogram, chest roentgenogram and ophthalmologic studies were performed during phases 1 and 4. Routine laboratory tests, lipid and lipoprotein analyses and determination of antinuclear antibody titers were performed at scheduled intervals.

TABLE III Supine Systolic and Diastolic Blood Pressure (in mm Hg) at Baseline, End of Titration Phase and End of Treatment

Baseline	Betaxolol (n = 71)	Atenolol (n = 75)
Supine		
systolic	147 ± 2	152 ± 2
diastolic	100 ± 1	101 ± 1
Decrease at end of titration*	**Betaxolol (n = 64)**	**Atenolol (n = 69)**
Supine		
systolic	14 ± 1	13 ± 2
diastolic	14 ± 1	11 ± 1
Decrease at end of treatment*	**Betaxolol (n = 57)**	**Atenolol (n = 60)**
Supine		
systolic	15 ± 1	11 ± 2
diastolic	13 ± 1	11 ± 1

* Data from each patient's last visit in the dose-titration and maintenance phases were used. Values are mean ± standard error. All values for dose titration and maintenance phases represent significant ($p < 0.01$) changes from baseline.

Patients were withdrawn from the study if any of the following occurred: average supine diastolic BP remained ≥105 mm Hg on 2 consecutive visits at the maximum dosage level, serious side effects, symptomatic bradycardia, a standing systolic BP <105 mm Hg, symptomatic orthostatic hypotension or poor compliance.

Statistical analyses: Changes in BP and heart rate at each visit were assessed by an analysis of variance incorporating treatment, center and their respective interaction. All available data from randomized patients at each visit were analyzed for efficacy. Side effects and laboratory parameters were evaluated in all 146 patients randomized to receive treatment. A conventional chi-square test was used for categorical analysis of percentage of patients responding to therapy in each treatment group. In addition, the cumulative percent of responders by treatment was plotted against natural log of dose at the end of titration and at the end of treatment period. The level of significance for all tests was set at $p < 0.05$. All values are expressed as the mean and 1 standard error.

Results

Patient population: One hundred forty-six patients were randomized to receive active therapy: 71 to betaxolol and 75 to atenolol. There were no significant differences in patient demographics between the 2 groups except for age (Table I). In both the betaxolol and atenolol groups, response rates did not differ significantly according to age. There was no difference in previous antihypertensive medications. After randomization, 14 patients receiving betaxolol and 15 patients receiving atenolol were withdrawn before completion of the treatment phase (Table II).

Antihypertensive effects: The time course of the BP-lowering effects of betaxolol and atenolol are

shown in Figure 1. Blood pressures at baseline, end of the titration and maintenance phases are listed in Table III. A significant reduction in BP occurred within 2 weeks from the start of active treatment in both groups and persisted throughout the 24-week treatment period. A comparison between treatment groups at weeks 4, 6, 10 and 12 showed that betaxolol significantly reduced supine diastolic BP to a greater degree compared with atenolol ($p < 0.05$) (Figure 1).

Discontinuation of active treatment and substitution of placebo (phase 4 withdrawal) resulted in an elevation of BP toward pretreatment levels with both drugs. After 2 weeks on placebo, supine diastolic and systolic BP increased by 10 ± 1 mm Hg and 14 ± 2 mm Hg, respectively, in the betaxolol group. Similarly, in the atenolol group, supine diastolic and systolic BP increased by 7 ± 1 mm Hg and 8 ± 2 mm Hg, respectively. For all response variables, the increase did not exceed pretreatment values.

Response rate: A significantly higher percentage of patients receiving betaxolol than those receiving atenolol achieved the targeted supine disastolic BP response (≤90 mm Hg or a reduction of ≥10 mm Hg). Of those patients completing the trial, 83% of the betaxolol group achieved the targeted response compared with 65% of the atenolol group ($p < 0.05$) (Figures 2 and 3). Normotension (supine disastolic BP ≤90 mm Hg) was achieved in 72% of the betaxolol group compared with 52% of the atenolol group ($p < 0.05$).

Heart rate: A significant reduction in heart rate from baseline value occurred in both groups during the first 2 weeks of treatment and persisted throughout the 24-week treatment period. At the end of the titration phase, supine heart rate for the betaxolol group was reduced by 10 ± 1 beats/min ($p < 0.01$) below the baseline value (75 ± 1 beats/min); for atenolol the reduction was 6 ± 1 beats/min ($p < 0.01$) below the baseline value (74 ± 1 beats/min). At the end of the maintenance phase, the supine heart rate was reduced by 11 ± 1 beats/min ($p < 0.01$) with betaxolol, and by 10 ± 1 beats/min ($p < 0.01$) with atenolol.

Side effects: All side effects elicited or volunteered by the patients or observed by the investigators were

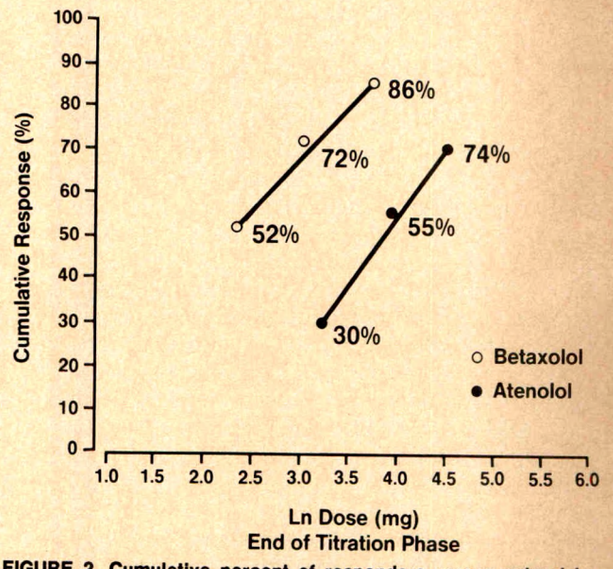

FIGURE 2. Cumulative percent of responders versus natural log (Ln) dose at the end of the titration phase. Response (%) = betaxolol 24.6 × Ln dose (mg) − 3.9; atenolol 31.0 × Ln dose (mg) − 67.8.

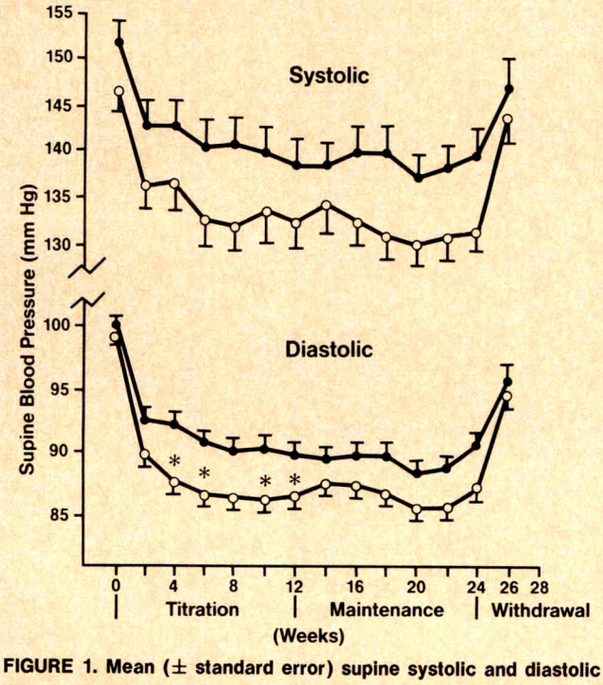

FIGURE 1. Mean (± standard error) supine systolic and diastolic blood pressure during treatment with betaxolol (○) and atenolol (●) in patients with mild to moderate essential hypertension. * $p < 0.05$ for betaxolol versus atenolol.

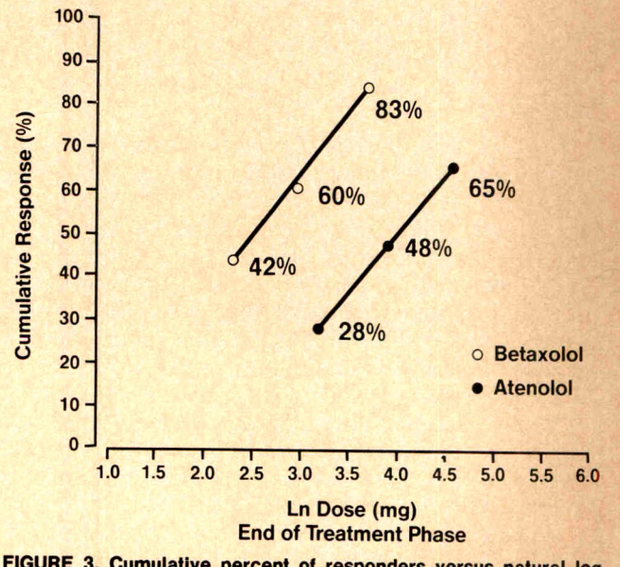

FIGURE 3. Cumulative percent of responders versus natural log (Ln) dose at the end of the treatment phase. Response (%) = betaxolol 24.3 × Ln dose (mg) − 2.9; atenolol 26.4 × Ln dose (mg) − 56.1.

recorded irrespective of their considered relation to treatment. There were no statistically significant differences in the type and incidence of side effects reported between groups. The most common side effects were bradycardia (<50 beats/min) (11 patients in the betaxolol and 9 in the atenolol group), fatigue (5 in the betaxolol and 3 in the atenolol group) and headache (6 in the betaxolol and 4 in the atenolol group).

Central nervous system side effects were similar. Depression occurred in 1 patient given each treatment. There was no difference in the incidence of sleep disturbances or impotence between groups.

Bradycardia occurred with a similar frequency in both treatment groups. Only 1 patient (in the betaxolol group) exhibited symptomatic bradycardia resulting in withdrawal from the study. The associated symptom in this patient was tiredness.

Laboratory abnormalities: There were no clinically significant changes from baseline in routine hematology, blood chemistries or urinalysis for patients treated with either drug. Three patients in the betaxolol group and 4 patients in the atenolol group developed positive antinuclear antibody titer test results, which were not associated with clinical symptoms.

No changes in total cholesterol, high density lipoprotein and low density lipoprotein were observed. There was a slight but not significant increase (10% from baseline) in serum triglycerides in the betaxolol group and a statistically significant ($p < 0.01$) increase (53% from baseline) in the atenolol group. The difference between treatment groups was not significant at either baseline or the end of the study. The baseline values were within normal limits for both groups.

Other clinical abnormalities: Several changes were observed in chest roentgenogram, electrocardiogram and ophthalmologic findings, but the relation to treatment was doubtful or uncertain. Ophthalmologic signs or ocular symptoms were noted in 3 patients in the atenolol group and 2 patients in the betaxolol group. No other clinical abnormalities were observed in any of these patients.

Discussion

The objective of this study was to compare the antihypertensive effects of betaxolol and atenolol 24 hours after administration. Both agents lowered BP over the dose ranges studied throughout the trial. At the end of the study, the percentage of patients responding was 83% for betaxolol and 65% for atenolol. The average dose among betaxolol responders was 20 mg and among atenolol responders was 52 mg; among all patients completing the study, the average dose at final treatment visit was 21 mg for betaxolol while for atenolol the average dose was 62 mg.

A consistently lower supine disastolic BP was observed with betaxolol at each treatment week of the trial. The observed results may be explained by the pharmacokinetic profile of the 2 drugs. The half-life of betaxolol (14 to 22 hours) should produce pharmacologic effects of a duration equal to or greater than its half-life. In contrast, while several studies[16–20] confirm that atenolol can provide BP control over a 24-hour dosing interval, its shorter half-life (6 to 7 hours) may cause the antihypertensive effect to diminish toward the end of a 24-hour period. This observation is supported by Warrington et al.[21] In their study, healthy volunteers received intravenous betaxolol, atenolol and propranolol. Hemodynamic indexes of β-adrenergic blocking effects were similar in magnitude at 2 and 4 hours after dosing, but at 24 hours, the pharmacologic effects of betaxolol were more pronounced than those of the other drugs studied. In another investigation, comparing single oral doses of betaxolol (40 mg), atenolol (200 mg) and propranolol (160 mg), the 24 hour β-blocking effects were reduced from the peak effects by 50% and 63% for atenolol and propranolol, respectively, whereas the β blockade for betaxolol diminished by only 9% over the 24-hour period.[22]

The side-effect profiles for betaxolol and atenolol were similar and consistent with those reported with other β-adrenergic antagonists. In particular, central nervous system side effects were low and similar between the 2 treatment groups. Although 3 patients in the betaxolol group and 4 in the atenolol group developed new and persistent positive antinuclear antibody titers during the study, these were not associated with symptoms. Further, in a recent study of diabetic hypertensive patients with elevated antinuclear antibody titers, subsequent antihypertensive treatment with betaxolol resulted in a decrease in these titers.[23]

It is desirable in the treatment of hypertension to achieve normotension (supine disastolic BP $\leq$90 mm Hg) and thereby influence the morbidity and mortality of the disease. Over the dose ranges studied, normotension was achieved in 72% of the patients who completed the trial with betaxolol. Also of interest was the rate of response to the initial dose of betaxolol. Of those patients completing the study, 50% achieved normotension or at least a 10 mm Hg reduction in supine disastolic BP with a single 10 mg dose of betaxolol.

In conclusion, this trial demonstrated that betaxolol may be more effective than atenolol when administered once daily to patients with mild to moderate hypertension when blood pressure is measured 24 hours after administration.

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Comparative Study of Primary Tissue Failure Between Porcine (Hancock and Carpentier-Edwards) and Bovine Pericardial (Ionescu-Shiley) Bioprostheses in the Aortic Position at Five- to Nine-Year Follow-Up

IGNACIO GALLO, MD, FRANCISCO NISTAL, MD, EMILIO ARBE, MS, and EDURNE ARTIÑANO, MD

Retrospective follow-up data on 458 consecutive patients who received a Hancock, Carpentier-Edwards (C-E) or Ionescu-Shiley (I-S) bioprosthesis in the aortic valve position between April 1978 and December 1981 are reviewed. A total of 461 valves (184 Hancock, 131 C-E and 146 I-S) were available for study of the incidence of primary tissue valve failure after 5 to 9 years of follow-up. Cumulative follow-up was 1,016 patient-years for patients with Hancock valve, 688 for the C-E and 767 for the I-S group. Of the 397 prostheses at risk (154 Hancock, 120 C-E and 123 I-S), 36 instances of primary tissue valve failure occurred (12 Hancock, 7 C-E and 17 I-S). On an actuarial basis, the calculated probability of freedom from primary tissue valve failure was 88 ± 4% for the Hancock group, 87 ± 6% for the C-E and 51 ± 17% for the I-S at 9 years. The linear incidence of tissue valve failure was 1.2 failing valves per 100 patient-years for the Hancock group, 1 for the C-E and 2.2 for the I-S. In a cohort of patients older than 40 years of age at the time of valve replacement, the rate of freedom from primary failure was 98 ± 1%, 87 ± 9% and 44 ± 22% for the Hancock, C-E and I-S groups, respectively, at 9 years. Comparison of actuarial curves disclosed a meaningful difference between the pericardial valve and the Hancock and C-E porcine bioprostheses at 9-year follow-up. These data should have some bearing of practical import not only when comparing different types of bioprostheses, but especially when recommending the appropriate valve replacement for the individual patient.

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Primary tissue failure is the main disadvantage in the long-term evolution of bioprosthetic cardiac[1-20] valves and the reason why many surgeons prefer mechanical valves in patients with a life expectancy >10 years.[4,5] The net 10-year results comparing the incidence of complications in patients receiving biologic or mechanical prosthetic heart valves, however, showed no significant difference between the 2 types of valves.[21,22] We evaluated the incidence of documented primary tissue failure among unselected patients included in 3 groups who underwent operation during the same period of time, by the same surgical team and who received either a porcine or bovine pericardial glutaraldehyde-preserved bioprosthesis in aortic position.

From the Servicio de Cirugía Cardiovascular and Departamento de Anatomía Patológica, Hospital Nacional "Marqués de Valdecilla," Facultad de Medicina, Universidad de Cantabria, Santander, Spain. Manuscript received August 26, 1987; revised manuscript received and accepted December 23, 1987.

Address for reprints: Ignacio Gallo, MD, Policlinica Guipuzcoa, Paseo Zorroaga, 20011 San Sebastian, Spain.

Methods

Patients: Between April 1978 and December 1981 a total of 458 patients, retrospectively reviewed, received in our institution a glutaraldehyde-preserved porcine (Hancock or Carpentier-Edwards [C-E]) or a bovine pericardial (Ionescu-Shiley [I-S]) bioprosthesis as valve substitute in aortic position. This analysis included a total of 461 valves (184 Hancock, 131 C-E and

TABLE I Follow-Up Data

	Hancock	Carpentier	Ionescu
Pts	182	130	146
Bioprostheses	184	131	146
Hospital mortality	15	8	15
Reoperations			
Paravalvular leak	9	2	4
Bacterial endocarditis	6	1	4
Prostheses at risk	154	120	123
Age (yr)			
Mean	49 ± 13	48 ± 12	50 ± 13
Patients <40 (%)	37 (24)	36 (30)	33 (27)
Patients >40 (%)	117 (76)	84 (70)	90 (73)
Range	18–70	17–71	15–73
Sex			
M (%)	104 (68)	87 (73)	62 (50)
F (%)	50 (22)	33 (27)	61 (50)
Cumulative follow-up (patient-years)	1,016	688	767
Degenerated valves	12	7	17
Linear incidence	1.2 ± 0.3	1 ± 0.4	2.2 ± 0.5

146 I-S) available for study of the incidence of primary tissue valve failure after 5 to 9 years of follow-up. No special selection or randomization was used to select the type of bioprosthesis to be implanted for each individual patient; only the surgeon's preference was a determinant in this respect. We excluded from this study all patients who were not discharged from hospital, and patients with valve failure caused by infection and paravalvular leaks. This study was limited to the 399 prostheses selected according to the stated criteria and controlled until April 1987. Table I lists the total number of valves placed and those selected for the study.

Operative techniques were standardized, and included cold ischemic arrest with topical hypothermia for myocardial protection, moderate systemic hypothermia and uninterrupted aortic crossclamping. Rinsing and perioperative handling of valves was similar in all cases, because all valves were implanted during the same time frame and by the same surgical team.

Primary tissue valve failure was established either at reoperation or autopsy by detection of valve regurgitation or stenosis due to construction failures, cuspal tears, perforation, calcific deposits or stiffening of the leaflets in the absence of a previous active infective process. Mechanical failures due to faults in construction were included. The endpoint for the definition of primary tissue failure was not only reoperation but also death with confirmation of valve failure by autopsy examination or previous positive diagnosis of dysfunction made clinically and hemodynamically. Living patients with hemodynamic or clinical diagnosis of valve dysfunction are not included because primary tissue valve failure has not been confirmed.

All surviving patients were routinely evaluated at this hospital. Those who failed to report to the hospital were contacted by letter. Follow-up was conducted until April 1987. Survival rates and the incidence of tissue valve failure are determined by actuarial analysis (Kaplan-Meier) and by linearized occurrence rates

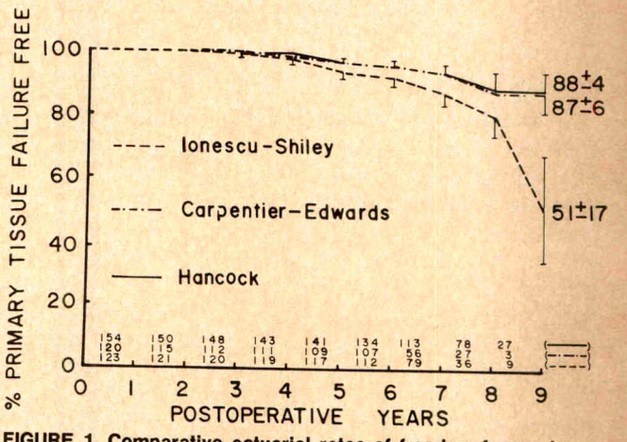

FIGURE 1. Comparative actuarial rates of freedom from primary tissue valve failure in Hancock, Carpentier-Edwards and Ionescu-Shiley bioprostheses at 9-year follow-up. The number of valves at risk per postoperative year is shown. Data are given as ± standard error.

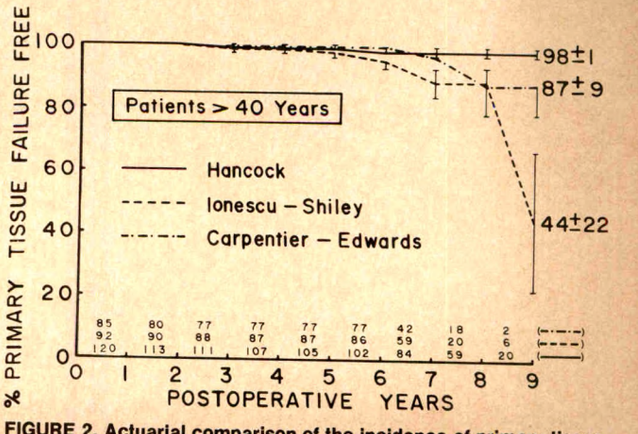

FIGURE 2. Actuarial comparison of the incidence of primary tissue valve failure in patients older than 40 years.

TABLE II Implantation Valve Sizes

	Hancock (n = 154)		Carpentier (n = 120)		Ionescu (n = 123)	
Size	No.	Failures per Size	No.	Failures per Size	No.	Failures per Size
19	3	—	—	—	16	2
21	6	—	—	—	37	6
23	46	3	23	1	37	6
25	48	2	41	1	13	3
27	29	2	35	5	13	—
29	15	3	11	—	5	—
31	7	2	10	—	2	—

and are given as ± 1 standard error of the mean. The comparison between different actuarial curves was performed using normal distribution. Differences were considered meaningful when the significance level was <0.05.

Explanted valves were examined, described and photographed macroscopically, processed by standard techniques for light microscopy and stained by hematoxylin/eosin.

Results

There were 397 valves at risk of primary tissue degeneration (154 Hancock, 120 C-E and 123 I-S). No differences in age, sex and other risk factors of primary tissue failure were observed according to the type of prosthesis.

Cumulative follow-up was 1,016 patient-years for patients with Hancock valves, 688 for the C-E group and 767 for the I-S.

Of the 397 prostheses at risk, 36 instances of valve degeneration, according to the previously expressed criteria, occurred in 36 patients followed for as long as 9 years. Twelve of the failed valves were Hancock (8% or 12 of 154), 7 C-E (6% or 7 of 120) and 17 I-S pericardial (14% or 17 of 123). Mean duration of the valves before being explanted was 68 ± 19 months (range 34 to 95), 63 ± 16 (47 to 93) and 68 ± 21 (36 to 104) for the Hancock, C-E and I-S valves, respectively, without significant differences. Linearized rates of primary valve failure were 1.2 ± 0.3 failing valves per 100 patient-years for the Hancock series, 1 ± 0.4 for the C-E and 2.2 ± 0.5 for the I-S. Mean age of patients whose valves degenerated afterwards was, at the time of implantation, 32 ± 11 years (range 20 to 55) for the Hancock group, 33 ± 10 (range 17 to 46) for the C-E and 41 ± 14 (range 15 to 62) for the I-S. Mean age of patients with failing valves was higher in the I-S series than in the porcine group, with a marginally significant difference ($0.05 < p < 0.1$). Distribution of bioprosthetic failures depending on valve size is listed in Table II.

On an actuarial basis the calculated probability of freedom from primary tissue valve failure was 88 ± 4%, 87 ± 6% and 51 ± 17% at 9 years of follow-up for the Hancock, C-E and I-S groups, respectively (Figure 1). A significant difference ($p < 0.05$) was observed in the last point of the curves between the porcine and pericardial prostheses, although both porcine series have a consistently higher rate of freedom from primary tissue valve failure starting at the fifth postoperative year. Freedom from degeneration was compared using actuarial analysis in a cohort of patients older than 40 years at the time of surgery (Figure 2). For the Hancock prostheses, the rate of freedom from primary tissue failure was 98 ± 1% at 9 years, 87 ± 9% for the C-E and 44 ± 22% for the I-S ($p < 0.01$). No statistically significant difference in the failure rates between C-E and Hancock porcine recipients was observed in this age group. Actuarial analysis of the incidence of primary tissue failure in patients younger or older than 40 years at the time of valve implantation showed a clear-cut difference among porcine valve recipients (Figure 3), with significantly higher failure rates in younger patients since the fifth postoperative year. However, patients with bovine bioprostheses showed no clear difference in failure rates depending on the age at the time of operation (Figure 4). The comparison of actuarial curves from different valve size cohorts yielded no

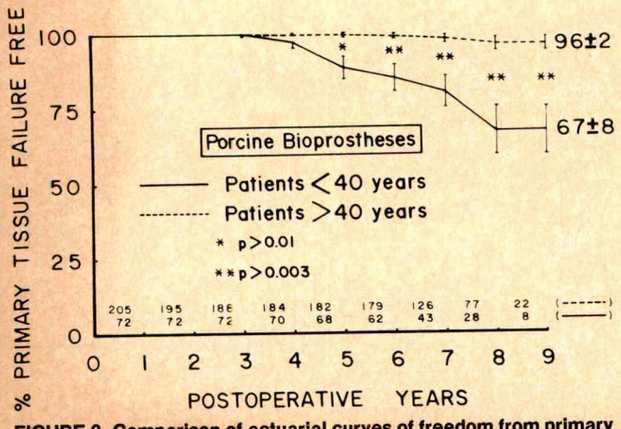

FIGURE 3. Comparison of actuarial curves of freedom from primary tissue valve failure in patients younger or older than 40 years with a porcine bioprosthesis.

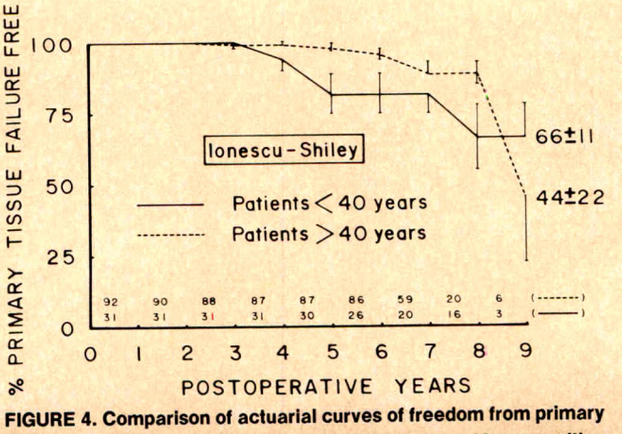

FIGURE 4. Comparison of actuarial curves of freedom from primary tissue valve failure in patients younger or older than 40 years with a bovine pericardial bioprosthesis.

significant difference of failure rates in either type of bioprosthesis.

The cause of valve failure in the pericardial group was tear and calcification in all cases. Calcification, from plaques to florid granulations, caused immobilization of leaflets and, when incompetent, cuspal tears were related with calcifications. Porcine bioprosthetic dysfunction was also associated with cuspal calcium deposits and calcium related tears.

Discussion

Tissue valve replacements for diseased heart valves have, as major advantages over mechanical prostheses, a low risk of thromboembolism, usually without anticoagulation, and therefore with a lower incidence of postoperative hemorrhagic accidents. Although limited durability is a problem with all current bioprostheses, this complication is often slow in onset, and therefore most patients with primary tissue valve failure may successfully undergo reoperation.

Dysfunction of the glutaraldehyde-preserved porcine xenografts, due to tissue degradation, has been extensively reported both in adult patients[1-6] and children.[7-14] In addition, the structural and ultrastructural study of surgically removed porcine bioprostheses has improved our knowledge of the pathogenesis of primary tissue failure and the recognition of several risk factors.[15-20] Primary tissue valve failure of the bovine pericardial xenografts has been reported in isolated cases,[23-39] and in some of them this valve failure was not caused by tissue degeneration or calcium.[35-39]

Comparison of the long-term results of different techniques of valve replacement is difficult because of the many factors that vary between surgical teams, such as patient population and surgical techniques. We have summarized a 9-year concomitant comparison of the incidence of tissue valve degeneration in a group of patients who underwent aortic valve replacement within the same institution, by the same surgical team, over a limited period of time, using porcine and bovine pericardial valves. This retrospective, nonrandomized study shows some advantages in terms of durability of the porcine valves. Preoperative data show no statistically significant differences in age and sex. Valve size distribution is very similar for both porcine series, the average being smaller in the pericardial group. Mean and cumulative follow-up times are very close in all groups and do not differ. Hospital and late deaths are not significantly different but its comparison and that of other events like thromboembolism, or reoperation rate for causes other than primary valve failure, does not constitute the purpose of this study.

Durability still remains as the major problem of tissue valves and a permanent concern for surgeons. Primary tissue valve failure of the Hancock porcine bioprosthesis has been extensively reported.[1-20] However, little information is available on the C-E and I-S durability in the intermediate and long-term period and, although many reports on porcine or pericardial bioprostheses describe the use of both types of valves, no specific comparison between them has been accomplished so far.[28]

Age of the patients at operation acts, in our own[1] and others[3,4,8,12] experience, as a factor that predisposes to primary tissue failure. The present results show that although this tendency is clearly demonstrated among porcine valve recipients, bovine pericardial valves display a completely different behavior in this respect. This phenomenon suggests that, even though younger age has a determinant effect on the appearance of primary tissue failure in porcine bioprostheses, other factors and specifically the intrinsic tendency of the bovine pericardial tissue to calcify may play a role in the latter group. These findings agree well with what has been previously observed both in patients[28-31] and experimental animals.[40] Mean age of patients with failing valves in this series was higher in the I-S group (41 ± 14 years) than in the Hancock (32 ± 11) or C-E (33 ± 10), with a marginally significant difference ($0.05 < p < 0.1$).

No risk factors for calcium (e.g., pregnancy, renal insufficiency) were found in any patient of either group with a failing valve. However, examination of actuarial curves shows no statistically significant difference, although the porcine series displays a consistently lower rate of freedom from primary tissue failure starting at the fifth postoperative year. One should be cautious when interpreting these results, but the origin of the bioprosthetic tissue (porcine aortic valve or bovine pericardium) has been recently considered a significant factor influencing the appearance of tissue degeneration in valves implanted in patients[28-31] and experimental animals.[40]

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Noninvasive Assessment of Mitral Stenosis Before and After Percutaneous Balloon Mitral Valvuloplasty

PATRICIA C. COME, MD, MARILYN F. RILEY, BS, RDMS, DANIEL J. DIVER, MD, JAMES P. MORGAN, MD, PhD, ROBERT D. SAFIAN, MD, and RAYMOND G. McKAY, MD

Thirty-seven patients with symptomatic mitral stenosis underwent balloon dilatation of the mitral valve. Significant increases ($p < 0.001$) were noted in both catheterization- and Doppler-determined valve area (0.9 ± 0.3 to 1.8 ± 0.8 and 0.9 ± 0.2 to 1.7 ± 0.5 cm^2). However, catheterization and Doppler areas before and after valvuloplasty correlated less well ($r = 0.51$, $p < 0.002$ and $r = 0.47$, $p < 0.005$, respectively) than the catheterization-Doppler area correlation in a previous study of 59 consecutive patients with varying degrees of mitral stenosis ($r = 0.84$, $p < 0.001$). Mitral valve area increases were independent of valve thickness estimated using 2-dimensional echocardiography. Flail mitral leaflet movement was not observed and the degree of mitral regurgitation qualitatively assessed using pulsed Doppler mapping techniques increased by >1 of 4 grades in only 1 patient. The lateral mitral valve orifice diameter increased more than the anteroposterior diameter, suggesting commissural splitting as the mechanism of successful valvuloplasty. Increases (all $p < 0.0001$) were noted in mitral valve EF slope (7 ± 5 to 18 ± 10 mm/s), excursion (11 ± 5 to 13 ± 4 mm), S20S interval (0.07 ± 0.02 to 0.08 ± 0.02 s) and cardiac output (4.2 ± 1.3 to 5.3 ± 2.0 liters/min). There were significant decreases (all $p < 0.001$) in left atrial diameter (5.4 ± 1.0 to 5.1 ± 1.0 cm), mean catheterization gradient (15 ± 5 to 8 ± 4 mm Hg) and mean Doppler gradient (10 ± 4 to 6 ± 3 mm Hg).

Thus, while Doppler study can accurately predict catheterization mitral valve area in patients referred for assessment of mitral stenosis, the correlation coefficients are lower in balloon valvuloplasty patients preselected for severe mitral stenosis and in patients after balloon valvuloplasty. Other noninvasive parameters, previously shown to be inaccurate predictors of baseline valve area, do reflect increases after valvuloplasty. Valvuloplasty can successfully increase valve area even in patients with severe mitral valve thickening and causes little change in the degree of mitral regurgitation.

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The development of successful percutaneous balloon mitral valvuloplasty[1–5] will undoubtedly increase the number of patients with rheumatic heart disease undergoing invasive diagnostic testing and therapeutic intervention. Imaging and Doppler echocardiography have been shown to be reliable noninvasive techniques for detecting rheumatic deformity of the mitral valve and for quantitating the severity of associated mitral stenosis and regurgitation.[6–16] The uses and limitations of echocardiography in defining the results of balloon valve dilatation, however, have not been fully defined. Accordingly, this study, including the 15 patients undergoing valvuloplasty at the Beth Israel Hospital in whom valvuloplasty techniques and initial findings have previously been reported,[3] was designed with 2 major objectives: to evaluate the accuracy of noninvasive techniques in determining the results of balloon valvuloplasty in patients with mitral stenosis and to determine the changes in valve appearance, mitral regurgitation, left atrial size and integrity of the interatrial septum following percutaneous mitral valve dilatation.

From the Charles A. Dana Research Institute and the Harvard-Thorndike Laboratory of Beth Israel Hospital, Department of Medicine (Cardiovascular Division), Beth Israel Hospital and Harvard Medical School, Boston, Massachusetts. This study was presented in part at the annual meeting of the American Heart Association, November 1987. Manuscript received September 29, 1987; revised manuscript received and accepted December 10, 1987.

Address for reprints: Patricia C. Come, MD, Cardiovascular Division, Beth Israel Hospital, 330 Brookline Avenue, Boston, Massachusetts 02215.

Methods

Patients: Between October 1985 and March 1987, 37 patients underwent balloon dilatation of the mitral valve for mitral stenosis at the Beth Israel Hospital. One of these patients, referred from another hospital for aortic valvuloplasty, was found by echocardiography to also have significant mitral stenosis. After severe stenosis of both valves was confirmed by hemodynamic measurements made immediately before valvuloplasty, both valves were dilated. Six additional patients considered for balloon valvuloplasty were rejected on the basis of echocardiographic study. In 3, imaging echocardiography detected thrombus in the appendage (2 patients) or the body (1 patient) of the left atrium, confirmed subsequently at operation. Based on echocardiographic studies, it was felt that 3 other patients, with prior catheterization diagnoses of severe mitral stenosis, had either no rheumatic mitral valve disease (2 patients) or insignificant mitral stenosis (1 patient with mitral valve area >1.5 cm^2). Repeat diagnostic catheterizations, with pulmonary capillary wedge pressures confirmed by the finding of wedge-position oxygen saturations equivalent to systemic arterial oxygen saturations, confirmed the echocardiographic findings. One of the 3 patients was found to have pulmonary venous obstruction localized to the right lower lobe.

The patients undergoing balloon valvuloplasty included 11 men and 26 women (mean age 55 ± 14 years). All had symptoms of pulmonary venous congestion, most commonly dyspnea on exertion. Noninvasive evaluation by imaging and Doppler echocardiography and echo-phonocardiography preceded valvuloplasty by 1 or 2 days. Repeat noninvasive evaluation was performed 2 to 4 days (all patients), 6 weeks (17) and 6 months (8) after valvuloplasty. Normal sinus rhythm, paced rhythm and atrial fibrillation were present in 22, 1 and 14 patients, respectively.

Phonocardiography: The aortic second sound to mitral valve opening interval was measured from echo-phonocardiograms obtained on an Irex System II. Valve opening was determined by the presence of an opening snap coinciding with the E point of the mitral valve echogram or from the E point alone when an opening snap could not be recorded.

M-mode and two-dimensional echocardiographic studies: M-mode echocardiograms were obtained using Irex System II, ATL Mark 600, or Hewlett-Packard 77020A echocardiographs. Two-dimensional and Doppler echocardiographic studies were performed with the ATL or Hewlett-Packard equipment. Mitral valve excursion was measured (in mm) as the maximal amplitude of the anterior diastolic movement of the anterior mitral leaflet.[17] The mitral valve EF slope was measured in mm/s. Maximal systolic left atrial diameter was measured using the leading edge to leading edge technique[17] from cursor-derived M-mode echocardiograms, with the sound beam oriented perpendicular to the long axis of the left atrium and left ventricle. If the cursor could not be oriented perpendicularly through the left atrium, systolic diameter was measured directly off the 2-dimensional screen. The left atrium, including the appendage, was carefully scanned for echogenic densities suggestive of thrombus.[18] Both M-mode and 2-dimensional echocardiograms were assessed for abnormalities of mitral valve movement typical of rheumatic deformity.[7,9-11] The degree of thickening of the valve and chordae tendineae was estimated from the 2-dimensional scans. Findings suggestive of a flail mitral leaflet, including high-frequency systolic fluttering or projection of a leaflet into the left atrium, were evaluated.[7] Attempts were made to visualize the mitral valve orifice in short axis.[9-11] To do so, the 2-dimensional transducer was placed in the second or third left intercostal space and angled to provide a parasternal long axis view. It was then rotated and angled inferiorly to provide a short axis view at the level of the papillary muscles. With slow superior transducer angulation, the mitral valve orifice at the tips of the mitral leaflets, where the area is generally smallest, was visualized. Transducer orientation was maximized to provide, when possible, true transverse rather than oblique views of the mitral orifice. The anteroposterior and lateral diameters of the mitral valve orifice were measured in the 30 patients in whom definition of anterior, posterior and lateral borders was possible both before and after valvuloplasty. In some patients, the edges of the mitral valve orifice could not be adequately visualized throughout all 360° of its circumference to permit optimal planimetry for determination of areas. In others, with severe pulmonary hypertension and resultant sizeable right heart dilation, the sound beam could not be directed perpendicularly through the left ventricle or mitral orifice. In addition, among those patients with marked chordal thickening, it was apparent that the limitation of leaflet separation might not be the only contributor to mitral inflow obstruction. Finally, prior echocardiographic studies had demonstrated that Doppler assessment of mitral valve area provides a reliable means of assessing the severity of mitral stenosis relative to catheterization[6,13,16,19] and may be the preferable technique in patients after surgical commissurotomy.[19] For these reasons, mitral valve areas were not planimetered from 2-dimensional short axis images.

Doppler echocardiographic studies: The magnitude of mitral regurgitation and stenosis was assessed using pulsed Doppler echocardiography. The left atrium was interrogated for regurgitation using parasternal long axis and apical 4- and 2-chamber views.[15,16] Trace to mild regurgitation was diagnosed if regurgitation could be recorded only at leaflet level or within the first third of the left atrium; moderate regurgitation was diagnosed if the signals extended to one-third to two-thirds of the length of the left atrium, generally over at least two-thirds of its width; and severe regurgitation was diagnosed when signals were obtained from even wider areas of the atrium.

For evaluation of mitral stenosis, the pulsed Doppler transducer was positioned at the apex to obtain 4- or 2-chamber apical views and the sample volume was placed on the ventricular side of the mitral valve. Using both audio and visual output, transducer position

and angulation were altered to record mitral inflow signals of highest velocity and narrowest spectral bandwidth (characteristics suggesting orientation of the sound beam in line with blood flow). Hard-copy recordings were made and digitized with a graphics tablet (GTCO) and microcomputer (IBM PC) using custom-written software (Datastat). Digitization consisted of tracing the velocity curves; from these velocity points for calculation of instantaneous pressures were obtained every 4 ms, permitting calculation of the mean pressure gradient. The pressure half-time was also calculated from the hard-copy recordings and mitral valve area (MVA) was estimated from the formula: MVA (cm^2) = 220/pressure half-time (ms).[13] The values reported for mean gradients and valve areas represent the average of values obtained from 10 beats. Special care was necessary to analyze the tracings from patients with atrial flutter[6] because increases in flow velocity are frequently seen after flutter waves on the ECG. If the slope of velocity decay was to be drawn to include velocity peaks caused by atrial contraction, underestimation of mitral valve area would have resulted. In such patients, therefore, only the initial slope was used to calculate valve area (Figure 1). In patients with atrial fibrillation or normal sinus rhythm, the downslope of the flow velocity signal was generally linear throughout diastole or until atrial contraction, respectively.

Color Doppler imaging was performed in 2 patients using a Toshiba SSH-65A phased array scanner. After mitral regurgitant area was visually assessed, both the width of the diastolic mitral inflow signal and the presence or absence of aliasing and of marked color variegation, typical of turbulent flow, were assessed before and after valvuloplasty.

Atrial septal defect flow was determined using pulsed Doppler, contrast echocardiography, or both.[13,20–22] For pulsed Doppler echocardiography, the sample volume was placed on the right atrial side of the interatrial septum, in the subcostal and parasternal right ventricular inflow tract views. Shunt flow from the left atrium to the right atrium was recognized by the presence of a continuous flow disturbance, usually maximal during late systole and late diastole, and directed toward the right atrium.[13,20] Contrast echocardiography was performed after the injection of agitated saline mixed with the patient's own blood into an antecubital vein. Imaging was performed during quiet respiration and during and after release of a Valsalva maneuver. A communication between right and left atria was diagnosed if there was a subsequent negative contrast effect in the right atrium or a positive contrast appearance in the left heart, or both.[21,22] All echocardiographic recordings were made by the senior technologist or the laboratory director. The measurements were made by a senior echocardiographer, unaware of results of any prior hemodynamic assessment.

Cardiac catheterization and valvuloplasty: Left and right heart catheterizations using a 7 Fr pigtail catheter and a 7 Fr balloon flotation catheter, respectively, were performed via the left femoral artery and left femoral vein. During right heart catheterization, a diagnostic oxygen saturation series was obtained. After placement of left and right heart catheters, measurements were made of systemic arterial, left ventricular, pulmonary capillary wedge and pulmonary arterial pressures. Pulmonary arterial and left ventricular oxygen saturations were determined. The pulmonary arterial catheter was then advanced to the pulmonary capillary wedge position, under hemodynamic monitoring. The presence of the catheter in the wedge position was confirmed by aspiration of blood with oxygen saturation equivalent to that of systemic arterial blood. Oxygen consumption was measured using a metabolic rate meter (Waters Instrument), and cardiac output was calculated using the Fick technique.

In the patients undergoing valvuloplasty, transseptal catheterization was performed following baseline hemodynamic measurements. After dilatation of the interatrial septum, balloon dilatation of the mitral valve was carried out using techniques described previously.[3] The balloon was inflated for 10 to 15 seconds; saline and a radiographic contrast agent (Angiovist) were used. Repeated inflations were performed until a waist in the balloon, created by the mitral valve, disappeared. Maximal balloon sizes were 23 mm (1 patient) and 25 mm (21 patients). Simultaneous inflations of 18 mm and 20 mm balloons were performed in 15 patients. Immediately after balloon valvuloplasty, all hemodynamic recordings and oximetric analyses were repeated. Mitral valve gradients were calculated from recordings of simultaneous pulmonary capillary wedge or left atrial and left ventricular pressures. The mitral valve areas before and after valvuloplasty were calculated according to the Gorlin formula. Left ven-

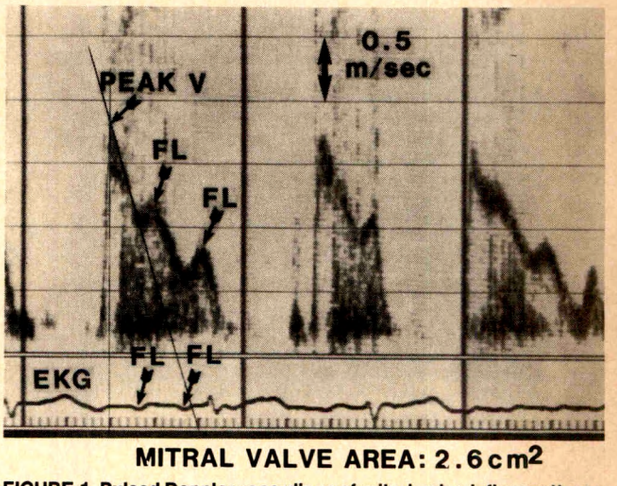

FIGURE 1. Pulsed Doppler recordings of mitral valve inflow patterns in a patient with atrial flutter (FL) indicate the increases in flow velocity (V) produced by atrial contractions. Reliable noninvasive estimation of mitral valve area was possible using the initial rapid diastolic slope. The atrial contributions to flow velocity are clearly seen in this patient, whereas in others it may be more difficult to separate the initial slope from intermittent flutter waves. An underestimation of valve area would occur if the slope of velocity decay was drawn to include the V peaks due to atrial contractions.

triculography was performed in only 9 patients both before and after valve dilatation. High pulmonary venous pressures or concomitant renal disease, or both, precluded the safe use of 2 doses of contrast in many of the other patients.

Twenty of the 37 patients undergoing valvuloplasty had had a diagnostic catheterization 1 to 3 months before valvuloplasty, generally at an outside referral hospital. This afforded the opportunity to assess the reproducibility of catheterization estimates of mitral valve areas. In all cases, cardiac outputs had been assessed using Fick or thermodilution techniques.

Statistical evaluation: Mean and standard deviation were determined for all variables. Correlations between variables were determined by the correlation coefficient and linearity was assessed by linear regression. Paired *t* testing determined the statistical significance of changes in parameters of valve function after valvuloplasty and also compared results of first and second prevalvuloplasty assessments of mitral valve area in patients having 2 catheterizations before valvuloplasty.

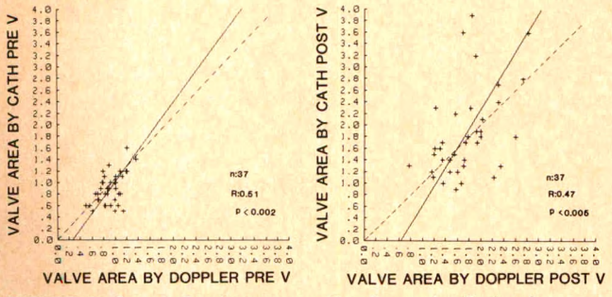

FIGURE 2. Correlation between estimations of mitral valve area made by Doppler pressure half-time techniques and catheterization assessments of mitral valve area before (*left*) and after (*right*) mitral valve valvuloplasty (V) in the group of 37 patients undergoing valvuloplasty for significant, symptomatic mitral stenosis.

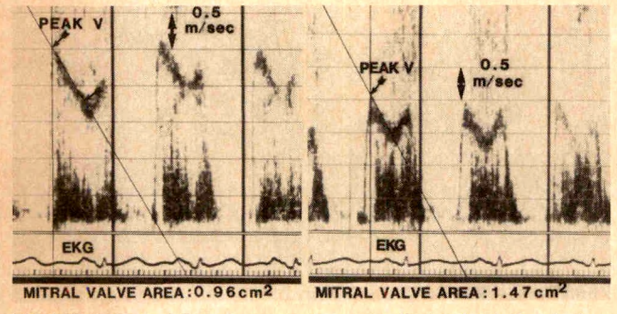

FIGURE 3. Pulsed Doppler recordings of mitral valve inflow before (*left*) and after (*right*) mitral valve dilation. Peak velocity (V) decreased from 2.55 to 2.1 m/s, mean gradient decreased from 16.5 to 9 mm Hg and Doppler-estimated mitral valve area increased from 0.96 to 1.47 cm². By catheterization, mitral valve area changed from 0.9 to 1.5 cm². The *unlabeled black arrows* indicate the velocity at pressure half-time. The *dark vertical lines* represent 1-second markers. EKG = electrocardiogram.

Results

Mild, mild to moderate and moderate to severe valvular thickening was noted on 2-dimensional echocardiography in 14, 5 and 18 patients, respectively. Moderate or severe subvalvular thickening, thought to represent dense fibrosis and fusion of chordae tendineae, was observed in 2 patients. In the 37 patients undergoing mitral valvuloplasty, prevalvuloplasty measurements of mitral valve area by Doppler and catheterization techniques were 0.9 ± 0.2 and 0.9 ± 0.3 cm^2, respectively ($r = 0.51$, $p < 0.002$) (Figure 2). After valvuloplasty, mitral valve areas—assessed by catheterization and Doppler techniques—increased in each patient, with group means increasing from 0.9 ± 0.3 to 1.8 ± 0.8 cm^2 and from 0.9 ± 0.2 to 1.7 ± 0.5 cm^2 (both $p < 0.001$). An example of the transmitral flow patterns before and after valvuloplasty in 1 patient is shown in Figure 3. The correlation coefficient for the relation between Doppler and catheterization area measurement following valvuloplasty was 0.47 ($p < 0.005$) (Figure 2). The mean absolute increases in catheterization or Doppler valve areas for the 14 patients with mild mitral thickening were not different from those in the 18 patients with moderate or severe thickening (1.1 ± 0.7 vs 1.0 ± 0.6 cm^2 by catheterization and 0.9 ± 0.6 vs 0.8 ± 0.4 cm^2 by Doppler, both p = not significant). The 2 patients with marked subvalvular thickening had catheterization-documented area increases of 0.6 and 1.2 cm^2.

No patient developed echocardiographic findings of a flail mitral valve. The diastolic short axis anteroposterior and lateral valve diameters increased significantly from 7.6 ± 1.8 to 9.8 ± 2.3 mm ($p < 0.001$) and from 12.6 ± 2.7 to 20.9 ± 3.5 mm ($p < 0.0001$), respectively (Figure 4). The absolute increase in lateral diameter, however, was significantly greater ($p < 0.0001$).

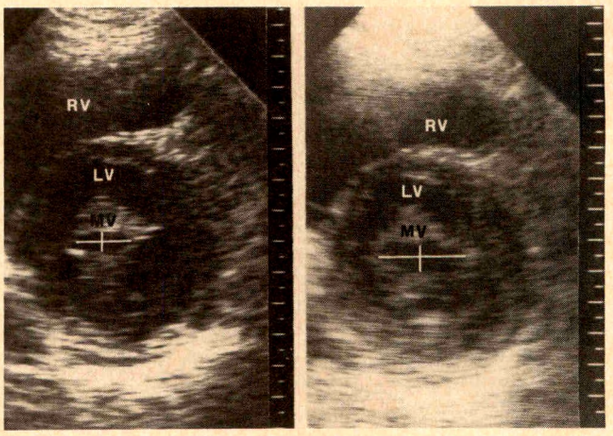

FIGURE 4. Short axis views of the diastolic mitral valve (MV) orifice before (*left*) and after (*right*) valvuloplasty. The anteroposterior diameter increased from 0.8 to 0.9 cm and the lateral diameter increased from 1.7 to 2.5 cm. Catheterization assessment of the mitral valve area revealed an increase from 0.9 to 3.6 cm². *Markings* on the right side of the pictures indicate 1 cm (longer horizontal markings) and 0.5 cm (shorter horizontal markings). LV = left ventricle; RV = right ventricle.

Mitral regurgitation was detected by pulsed Doppler echocardiography in 24 of the 37 patients before balloon valvuloplasty and in 24 patients after it (Figure 5). An increase of >1 grade of regurgitation was noted in only 1 patient. Ventriculography performed both before and after valvuloplasty in only 9 patients revealed an increase in mitral regurgitation of >1 grade in 2 patients. Seven patients had either no regurgitation on either study (5 patients) or no change from a prevalvuloplasty pattern of mild mitral regurgitation (2).

No patient had an evident atrial septal defect before valvuloplasty. However, an interatrial communication was detected after valvuloplasty in 12 patients by contrast, Doppler echocardiography, or both (Figure 6) and in 9 patients by oximetry (mean Qp/Qs = 1.6, range 1.1 to 2.3). Echocardiographic and oximetric diagnoses of the presence or absence of an atrial septal defect were concurrent in 30 patients. One shunt (Qp/Qs = 1.2) was not detected by noninvasive study and in another patient noninvasive evaluation of the integrity of the interatrial septum was inadvertently omitted from study. Five patients with echocardiographic findings of a left-to-right shunt had no diagnostic oxygen step-up (i.e., <2 volumes %) in the right heart.

Following valvuloplasty, there were increases (all p <0.0001) in EF slope (7.4 ± 4.9 to 18.3 ± 10.2 mm), valve excursion (10.7 ± 4.9 to 12.9 ± 4.3 mm/s), and aortic second sound to opening snap interval (0.07 ± 0.02 to 0.08 ± 0.02 s) (Figure 7). Decreases or no change were seen in 5 of 37, 10 of 37 and 10 of 35 patients, respectively. There were decreases (all p <0.0001) in left atrial diameter (5.4 ± 1.0 to 5.1 ± 1.0 cm), mean catheterization gradient (15 ± 5 to 8 ± 4 mm Hg) and mean Doppler gradient (10 ± 4 to 6 ± 3 mm Hg). Increases or no change in values were seen in 8 of 37, 6 of 37 and 6 of 37 patients, respectively. Cardiac output increased (4.2 ± 1.3 to 5.3 ± 2.0 liters/min, p <0.0001) in 33 of 37 patients.

In the 23 patients undergoing valvuloplasty who had had 2 prevalvuloplasty measurements of valve area by catheterization, there was a significant corre-

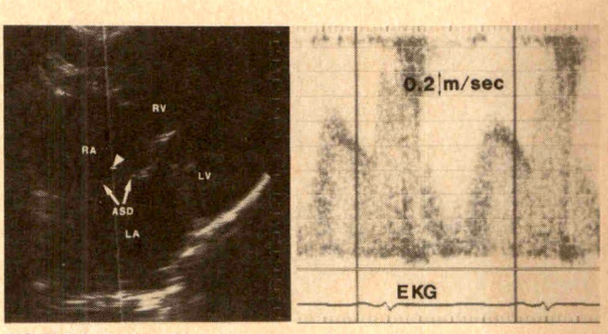

FIGURE 6. Pulsed Doppler interrogation of the interatrial septum in the subcostal 4-chamber view (*left*) demonstrates a continuous flow disturbance (*right*) directed toward the transducer and characteristic of left-to-right shunt flow through an atrial septal defect (ASD) created by transseptal catheterization and dilatation of the interatrial septum for passage of dilatation catheters. EKG = electrocardiogram; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

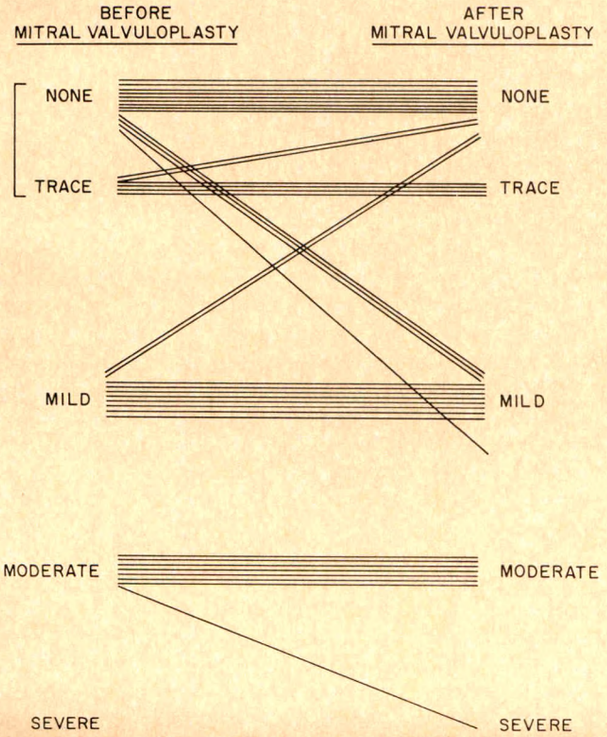

FIGURE 5. Grade of mitral regurgitation before (*left*) and after (*right*) mitral valvuloplasty.

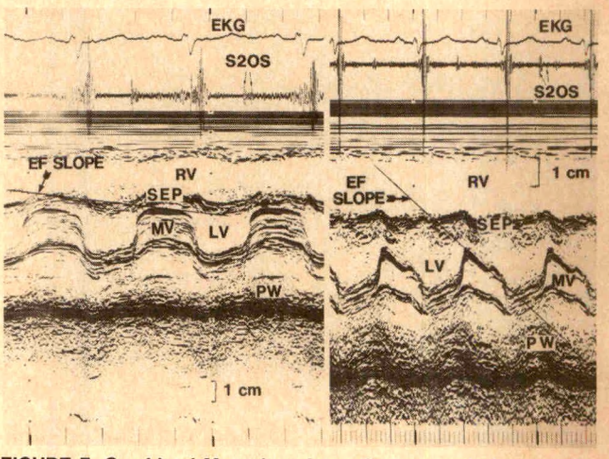

FIGURE 7. Combined M-mode echocardiogram and phonocardiogram in a patient before (*left*) and after (*right*) valvuloplasty. The catheterization- and Doppler-estimated mitral valve area increased from 1.4 to 2.4 and from 1.4 to 2.3 cm², respectively. The excursion of the anterior mitral valve (MV) leaflet did not change but the EF slope increased from 10 to 40 mm/s. The aortic second sound to opening snap (S2OS) increased from 0.04 to 0.07 seconds. The paper speeds in the 2 recordings differ; the distance between the vertical calibration dots denotes 1 second. EKG = electrocardiogram; LV = left ventricle; PW = posterior wall; RV = right ventricle.

lation between the first and the second measurements ($r = 0.74$, $p < 0.001$) (Figure 8).

Analysis by color Doppler (Figure 9) revealed a narrow diastolic mitral inflow jet before valvuloplasty, with a variegated color pattern indicating turbulent flow and aliasing reflecting high flow velocity. After valvuloplasty, the flow jet through the less stenotic valve was wider and had a fairly homogeneous color spectrum, indicating lower blood flow velocity and a lesser degree of turbulence (Figure 9).

In the 17 patients restudied by echocardiography 6 weeks after valvuloplasty, the mean mitral valve area assessed by pressure half-time techniques was unchanged from that on the first study carried out after valvuloplasty (1.6 ± 0.4 vs 1.6 ± 0.4 cm^2, p = not significant). Valve areas in 8 patients restudied by Doppler 6 months after valvuloplasty also were unchanged from the first postvalvuloplasty study (1.5 ± 0.3 vs 1.6 ± 0.3 cm^2, difference not significant).

Discussion

Because of its initial success and low complication rate,[2-5] balloon mitral valve dilatation will likely become widely used for the treatment of symptomatic patients with mitral stenosis. Because diagnostic catheterization is costly and has a definite, albeit small, associated morbidity and mortality, there is a need for noninvasive techniques permitting accurate quantitation of the severity of mitral stenosis and assessment of short- and long-term results of valve dilatation.

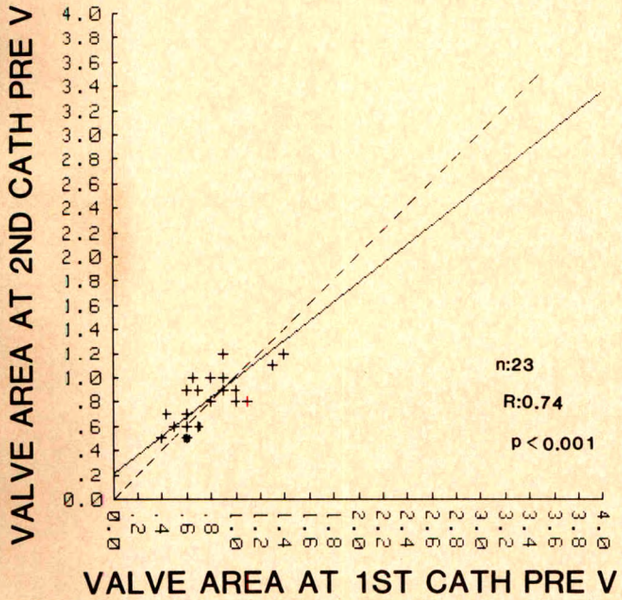

FIGURE 8. Correlation between 2 prevalvuloplasty values for catheterization mitral valve areas in the 23 patients in whom a diagnostic catheterization preceded the catheterization performed for purpose of valvuloplasty (V) by less than 3 months. Excluded from the figure are those patients referred with a catheterization diagnosis of severe mitral stenosis but found to have mild mitral stenosis.

A previous study from our institution of 59 consecutive patients with rheumatic mitral valve disease[8] indicated a close correlation ($r = 0.84$, $p < 0.001$) between noninvasive and catheterization determinations of mitral valve area and confirmed findings of several previous smaller studies in which Doppler echocardiography was shown to reliably quantitate the severity of mitral stenosis.[6,13,14,19] The accuracy of Doppler studies should enable catheterization for diagnostic purposes to be largely eliminated. Most patients, except those with suspected coronary arterial pathology or aortic valve disease (not adequately defined by noninvasive techniques), could undergo a single cardiac catheterization procedure, with standby for valvuloplasty if the noninvasive findings were supported. The savings in cost from the elimination of 1 catheterization and the associated in-patient days would be considerable. In addition, the total morbidity and mortality associated with catheterization would be reduced. In 1 of our patients, mitral valvuloplasty was delayed for weeks due to femoral vein thrombosis following diagnostic catheterization. Another patient, not included in our series, had persistent femoral venous thrombosis after diagnostic catheterization, making valvuloplasty impossible.

The importance of actual calculations of mitral area has been emphasized in the previous study from our institution of 59 consecutive patients with rheumatic mitral valve diseases.[8] Although significant correlations were found between catheterization mitral valve area and other noninvasive parameters, including EF slope ($r = 0.36$, $p < 0.01$), valve excursion ($r = 0.47$, $p < 0.001$), aortic second sound to opening snap interval ($r = 0.46$, $p < 0.001$) and mean mitral gradient ($r = -0.54$, $p < 0.001$), the wide scatter of data points, reflected by the low r values, does not permit their use as indicators of stenosis severity.[8] Because those measurements depend upon multiple factors in addition to valve area, such findings were not surprising. The mean diastolic gradient, for example, also depends upon forward cardiac output, mitral regurgitation, duration of diastole and the contribution of atrial systole. The aortic second sound to opening snap interval is also dependent on left atrial pressure at the mitral valve opening, heart rate, mitral valve stiffness, rate of left ventricular relaxation and the pressure at which the aortic valve closes.[23] The EF slope also depends on cardiac output, transducer angulation, coexisting ventricular disease, heart rhythm and the structural characteristics of the valve itself.[7] Finally, the recorded anterior leaflet excursion varies depending upon which portion of the leaflet is transected by the sound beam.[7]

It is of interest that the degree of valve thickening in our valvuloplasty patients did not correlate with the success of dilatation. Our experience supplements both case reports[24,25] of successful dilatation of heavily calcified mitral valves and an in vitro study in which balloon-induced increases in valve area were unrelated to the extent of calcific deposits on a roentgenographic study.[26] These findings suggest that attempted

percutaneous mitral valve dilatation need not be restricted to those patients with only mild valve fibrosis. They, however, contrast with findings suggesting reduced efficacy of surgical commissurotomy in patients with highly fibrotic and calcific mitral valve disease[27-31] and with studies from other institutions suggesting lesser short- and long-term efficacy of percutaneous valve dilation in patients with severe leaflet fibrosis and calcification.[32-34] The predictive role of echocardiography in identifying optimal patients for valvuloplasty requires further study.

Another major role for noninvasive testing in centers performing percutaneous valvuloplasty will be confirmation of the presence and severity of mitral stenosis in patients referred for valvuloplasty. In this regard, our echo findings of either no rheumatic disease or of mild mitral stenosis (valve area >1.5 cm^2), confirmed by repeat catheterization in our laboratory, in 3 patients referred with catheterization diagnoses of severe mitral stenosis are disturbing in that they suggest that some patients may be undergoing unindicated, aggressive therapy, including valvuloplasty and mitral valve replacement.

Another role of echocardiography reflects its ability to define intracardiac pathology in addition to mitral stenosis. The presence and severity of aortic stenosis

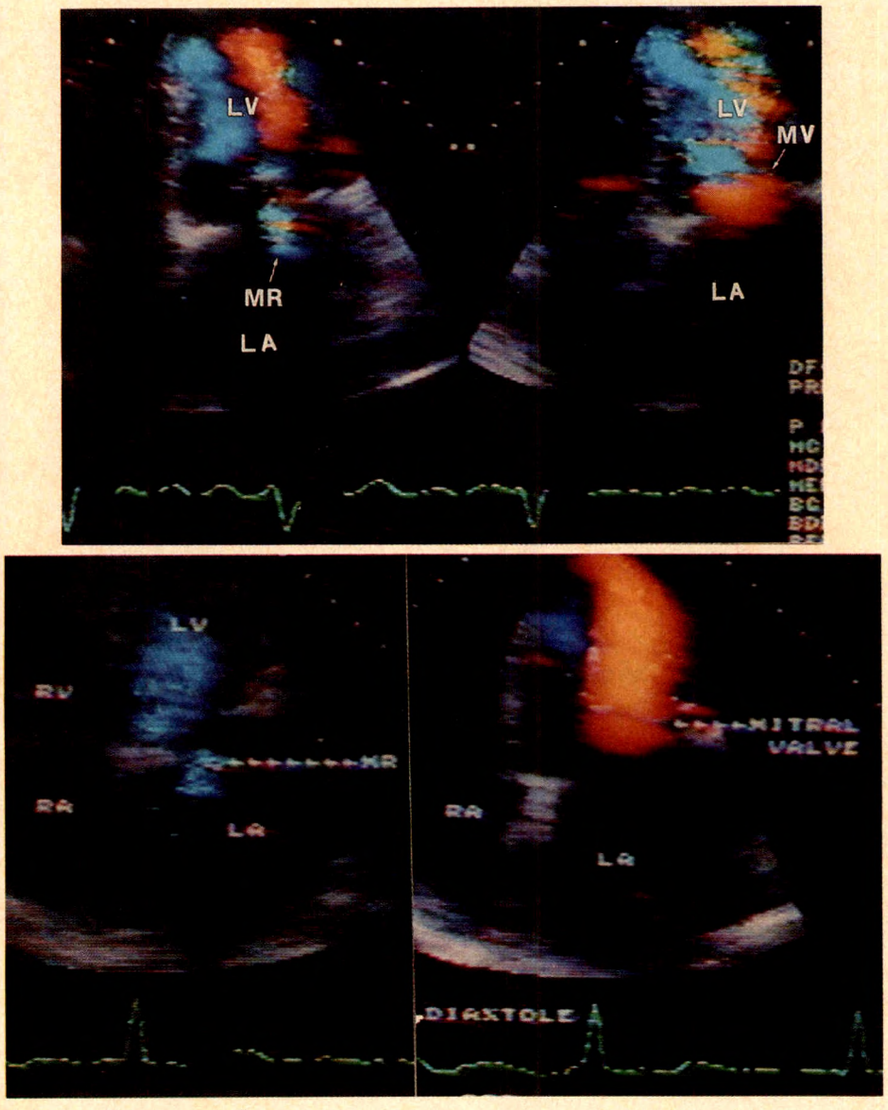

FIGURE 9. Color-coded pulsed Doppler recordings obtained with transducer placement at the left ventricular apex before valvuloplasty in systole (*upper left*) and diastole (*upper right*) and after valvuloplasty in systole (*lower left*) and diastole (*lower right*). The magnitude of mitral regurgitation (MR) in the left atrium during systole appears unchanged. Before valvuloplasty, the mitral valve inflow jet had a variegated color pattern (indicating turbulent flow) and aliasing (pointing to high flow velocity). After valvuloplasty, the width of the inflow signal at the level of the mitral valve orifice is far wider and the signal has a fairly homogeneous color spectrum, indicating both lower flow velocity and a lesser degree of turbulence.

can be quite accurately defined using the continuity equation.[35,36] In addition, the presence and relative magnitude of aortic insufficiency and mitral regurgitation and the status of left ventricular systolic performance can be evaluated. While color Doppler echocardiography may be preferable to routine pulsed Doppler echocardiography in estimating the severity of regurgitation, especially if regurgitant jets are eccentric, careful pulsed mapping of the entire left atrium in several planes (as performed in our study) permits detection and gross quantitation of regurgitant severity and, most importantly, allows comparison with prevalvuloplasty assessments. The number of patients undergoing both pre- and postvalvuloplasty ventriculography was small. However, the limited results from our institution suggest that sizable increases in mitral regurgitation are uncommon. In the present study, Doppler estimates of severity of regurgitation were very similar to the ventriculographic assessments. Full noninvasive definition of other pathology is particularly important in patients with high baseline pulmonary capillary wedge pressures, in whom the use of hyperosmolar contrast agents for ventriculography or aortography, or both, may precipitate pulmonary edema, and in patients with renal dysfunction. Echocardiography can also be used to detect left atrial thrombi within the body or appendage of the left atrium.[18] Their presence, as in the 3 patients denied valvuloplasty, is considered a relative contraindication to valvuloplasty using the transseptal approach.

Finally, echocardiography promises to be a useful technique for defining both the short- and long-term results of percutaneous mitral valve dilatation. Chordal and leaflet tears were not apparent in our study, as assessed by abnormalities of leaflet movement, and the greater increase in lateral rather than in anteroposterior dimension of the diastolic valve orifice was compatible with pathologic findings indicating that successful valvuloplasty involves splitting of previously fused commissures.[3,26,27] Doppler mapping of mitral regurgitant jets provides evidence that successful dilatation may usually be accomplished without appreciable increases in mitral regurgitation. Contrast and 2-dimensional echocardiography are sensitive techniques for detection of left-to-right shunting through the hole created in the interatrial septum for passage of the dilatation catheter. Serial studies should permit analysis of whether these defects close over time, and, in appropriate patients such as those without pulmonary or aortic regurgitation, may permit serial quantitation of the Qp/Qs ratio over time. Because right ventricular and, therefore, pulmonary arterial systolic pressure (in the absence of pulmonary stenosis) can be estimated from flow velocities in tricuspid regurgitant jets, Doppler echocardiography may additionally permit study of the rate of regression of pulmonary hypertension in patients after successful dilation.

Obviously, the most important parameter to be evaluated is that of mitral valve area. In our study mitral valve area measured by both catheterization and Doppler techniques increased in each patient after valvuloplasty, indicating the ability of echocardiography to detect a reduction of the severity of mitral stenosis. It is disappointing, however, that the coefficients of correlation for the relation between Doppler mitral valve areas and catheterization mitral valve areas were lower than that of 0.84 noted in our larger, unselected series of 59 patients previously reported.[8] In the group before valvuloplasty, the r value of only 0.51 may reflect the fact that the range of valve areas was very small, with each patient having severe mitral stenosis.

Reasons for the discrepancy between catheterization and Doppler assessments of mitral valve area after valvuloplasty probably include the following: lower accuracy of catheterization-planimetered gradients when gradients are small; inaccuracies in using the Fick cardiac output in the Gorlin determination of mitral valve area in patients with mitral regurgitation or left-to-right shunts across the created atrial septal defects; and decreased accuracy of Doppler calculation of mitral valve area in the setting of relatively large mitral areas, probably related to the steep rates of velocity fall-off. Wilkins[38] and Reid et al[39] noted very poor correlations between Doppler and catheterization determinations of mitral valve area when measurements were made immediately after or within the first 24 hours after balloon valvuloplasty. Thomas et al[40] suggested that alterations after valvuloplasty in left atrial pressure and compliance may adversely affect this correlation. Their studies, performed within the first 24 hours after valvuloplasty, reported pressure half-time measurements based on an average of only 1 to 3 beats. The greater accuracy of postvalvuloplasty pressure half-time valve areas relative to catheterization in our study could reflect a longer delay (48 to 96 hours) between valvuloplasty and echocardiographic evaluation, or the fact that our reported Doppler areas represent mean areas calculated from 10 different beats in normal sinus rhythm or in atrial fibrillation. The longer delay time may be of importance, since Reid et al[39] demonstrated a much closer correlation between catheterization and Doppler areas 3 months after valvuloplasty.[39] The lack of planimetered mitral valve areas in our study is an obvious weakness and further work will be necessary to determine if the planimetry technique or the pressure half-time assessment provides more accurate determination of mitral valve area in short- and long-term follow-up. The limitations of catheterization techniques in area determination also must be emphasized. In the presence of mitral regurgitation, the Gorlin formula will underestimate valve area if Fick determinations of cardiac output are used. Although angiographic stroke volume would be preferable, it would be of limited use in mitral stenosis patients who also have aortic insufficiency or in whom high wedge pressures may contraindicate the use of relatively large amounts of contrast.

Finally, significant directional changes in left atrial size, mitral valve gradient, EF slope, mitral valve excursion and second sound to opening snap interval accompany successful valvuloplasty. In patients in whom valve area calculations via planimetry and Doppler techniques are not feasible, serial changes in

a combination of these parameters may permit a gross means of follow-up to supplement history, physical examination and routine roentgenographic and electrocardiographic evaluations.

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Angina Pectoris and Coronary Artery Disease in Severe Aortic Regurgitation

PHILIPPE TIMMERMANS, MD, JOS L. WILLEMS, MD, JAN PIESSENS, MD, and HILAIRE DE GEEST, MD

A consecutive series of 198 patients (148 men and 50 women, mean age 51 years, range 18 to 76) with pure, isolated, severe aortic regurgitation was retrospectively studied to determine the prevalence of angiographically significant coronary artery disease (CAD) and its relation to angina pectoris and coronary risk factors. Significant CAD (coronary diameter stenoses >50%) was found in 28 patients (14%). Typical angina was present in 18% and atypical chest pain in 16%. Angina alone had a sensitivity of 57% to detect significant CAD. The predictive accuracy of a positive history of angina was 46% and that of a negative test 93%. By using multivariate logistic regression, a risk score could be calculated that increased the sensitivity to 74% at equal specificity. Almost 40% of the total population had a risk score of <−2.9 (only 1 patient in this group had CAD). It is concluded that coronary arteriography can safely be omitted in many patients with severe aortic regurgitation if they have no symptoms of myocardial ischemia or risk factors known to increase its incidence.

(Am J Cardiol 1988;61:826–829)

Patients with severe aortic regurgitation (AR) often have a history of chest pain compatible with angina pectoris. It sometimes is even one of the first symptoms. However, there is significant controversy in the reported prevalence of angina pectoris and associated coronary artery disease (CAD).[1–5] As a result, disagreement exists with respect to the diagnostic workup of these patients. Some investigators recommend coronary arteriography only for patients with angina pectoris[1–3] whereas others advocate this examination for all cases irrespective of complaints.[4,5] Such conclusions were based on studies with relatively small sample sizes and assessed via univariate analysis only. The present study reviews clinical and cardiac catheterization findings in 198 cases seen in our institution.

Methods

Patients: All cardiac catheterizations performed between January 1972 and August 1986 were retrospectively reviewed starting from a computerized data base.[6] A total of 198 patients (148 men and 50 women; mean age 51 years, range 18 to 76) were selected because they fulfilled the criteria for severe AR without any concomitant valvular disease. AR was graded from the aortic angiogram on a scale from 1 to 4. Trivial or grade-1 AR was defined as a puff of dye entering the left ventricle during diastole. For grade 2, significantly more dye regurgitation was required, without complete filling of the left ventricle. Complete filling was needed for grade 3. Grade 4 consisted of complete opacification in the first diastole after injection, with contrast material remaining in the left ventricle for several beats. Only cases with AR of grade 3 (n = 83) and 4 (n = 115) were included in the present study. All patients with a peak-to-peak systolic gradient across the aortic valve of >10 mm Hg were excluded. Over the last decade, coronary arteriography is routinely performed in our institution during cardiac catheterization of patients with valvular heart disease and >30 years of age. In patients <30 years of age it is performed only when manifest chest discomfort compatible with angina pectoris is present.

Cardiac catheterization: Right- and left-sided cardiac catheterization, left ventriculography, aortography and selective coronary angiography were performed in all 198 patients. Left ventriculography was performed in the right anterior oblique projection and aortography in the left anterior oblique projection. Se-

From the Departments of Cardiology and Medical Informatics, University Hospital Gasthuisberg, Leuven, Belgium. Manuscript received August 17, 1987; revised manuscript received and accepted November 23, 1987.

Address for reprints: Hilaire De Geest, MD, Department of Cardiology, University Hospital Gasthuisberg, 49 Herestraat, 3000 Leuven, Belgium.

lective coronary arteriography was carried out in multiple projections using the Sones technique. Since April 1975 all coronary angiograms are standardly coded in our institution by means of a CAD-reporting system.[7] Significant CAD was defined as >50% diameter reduction of a major coronary artery or its side branches.

Clinical findings: The medical records pertaining to all cases were reviewed to determine the presence and characteristics of angina pectoris, atypical chest pain, dyspnea, palpitations, fatigue, vertigo or syncope. The following variables were also recorded on data collection forms: smoking habits, family history of CAD, personal history of hypertension, diabetes or myocardial infarction, body weight, height, serum cholesterol, hematocrit and use of diuretics or digitalis. The Canadian classification was used to grade angina pectoris and the New York Heart Association (NYHA) to grade the functional status. For arterial hypertension a diastolic pressure of >90 mm Hg was required. Typical angina pectoris was defined as substernal discomfort or left precordial pain precipitated by exertion, emotional stress or exposure to cold, which was promptly relieved by rest or nitrates. Cases with nocturnal angina and typical angina at rest were also included. Patients with atypical chest pain, however, were not considered as having angina pectoris.

Statistical analysis: Bivariate analysis was used in frequency distributions and cross-tabulations of all variables made first for the total group and then, separately, for both sexes and for patients with and without significant CAD. Differences were tested using the chi-square analysis (with Yates correction) and Fisher exact test for categorical variables and the Student *t* test for quantitative variables using the SAS statistical package.[8]

For multivariate analysis, stepwise logistic regression was used to derive a prediction model with parameters significantly related to CAD. A multivariate risk score was calculated to stratify patients into either CAD or non-CAD. Standard methods were applied to derive sensitivity, specificity and the predictive values of a positive and negative test result.[9]

Results

Bivariate analysis results: Thirty-five patients (18%) had typical angina pectoris (29 class I or II and 6 class III or IV) and 32 (16%) had atypical chest pain. Dyspnea on exertion was present in 111 patients (56%) and palpitations in 50 (25%). Dyspnea was grade III or IV in 32.

Significant CAD (coronary diameter stenoses > 50%) was present in 28 patients (14%; 17 men and 11 women). In the so-called non-CAD group, 19 patients had minor narrowing of 1 or more coronary arteries and 151 patients (76%) presented with complete normal arteries (n = 170). The patients with CAD were significantly older (mean age 58 versus 50 years; p <0.005). The youngest case with CAD was a 27-year-old female with familial hypercholesterolemia and presenting with significant 2-vessel disease. In the CAD group, 14 patients had 1-vessel disease, 5 had 2-vessel disease and 8 had 3-vessel disease. One patient had significant left main disease.

TABLE I Clinical Characteristics of Patients with Aortic Regurgitation With and Without Significant Coronary Artery Disease

Variable	CAD Absent (n = 170)	CAD Present (n = 28)	p Value
Mean age (yrs)	50 ± 12	58 ± 11	0.005
Mean total cholesterol (mg/dl)	221 ± 64	247 ± 63	0.042
History of SH	22 (13%)	15 (54%)	0.001
Family history of CAD	47 (28%)	11 (39%)	NS
Diabetes mellitus	6 (4%)	1 (4%)	NS
Total cholesterol >240 mg/dl	47 (28%)	14 (52%)	0.02
Use of diuretics	61 (37%)	16 (59%)	0.03
Cigarette smokers	58 (34%)	9 (32%)	NS
Ex-cigarette smokers	35 (21%)	10 (36%)	NS

CAD = coronary artery disease; NS = not significant; SH = systemic hypertension.

TABLE II Performance of a Multiple Logistic Risk Score for Prediction of Significant Coronary Artery Disease in Patients With Severe Aortic Regurgitation

	Multiple Logistic Risk Score*			
CAD	<−2.92	<−2.00	>−1.35	>−0.65
Absent	76/162	124/162	19/162	9/162
	47%	77%	12%	6%
Present	1/27	3/27	20/27	16/27
	4%	11%	74%	59%
Predictive value	76/77	124/127	19/39	16/25
	99%	98%	49%	64%

* Risk score coefficient = −7.82 + 0.082 age (years) + 0.329 (sex: male = 1; female = 2) + 1.669 angina (yes = 1; no = 0) + 1.089 (sex × hypertension) + 1.607 (smoking × cholesterol >240 mg/dl).

A distribution of some clinical characteristics is given in Table I. The CAD group was not only older (p <0.005) but also had more hypertension (p <0.01) and total cholesterol (p <0.04). Patients with CAD had more frequently a positive family history of CAD, although this difference was not significant. There were more ex-cigarette smokers in the CAD group, but this also was not statistically significant.

Relation between angina pectoris and coronary artery disease: Of the 28 patients with CAD, 16 proved to have typical angina pectoris, which resulted in a sensitivity of 57% for this symptom. However, 19 patients from the 170 without significant CAD also had typical angina, giving a specificity of 89%. From these data a positive predictive value of 46% (16 of 35) can be derived for angina. The absence of angina (the predictive value of a negative test) correctly predicted absent CAD in 93% (151 of 163).

Multivariate analysis: By means of multiple logistic regression a risk score could be calculated based on angina pectoris, age, sex, smoking habits, history of hypertension and serum cholesterol to predict the presence and absence of significant CAD (Table II).

TABLE III Prevalence of Angina Pectoris and Significant Coronary Artery Disease in Patients With Angiographically Proven Severe Aortic Regurgitation

Reference	No.	CAD	Angina Pectoris
Basta et al, 1975[1]	20	—	10 (50%)
Graboys and Cohn, 1977[2]	29	4* (14%)	18 (62%)
Hakki et al, 1980[4]	31	11 (36%)	8 (26%)
Pathak et al, 1986[5]	78	29 (37%)	36 (46%)
Current study	198	28 (14%)	35 (18%)

* CAD defined as coronary diameter stenoses ≥75%; in all other studies 50% narrowing was used.

Due to missing values in some variables the analysis could only be performed for 189 cases, 27 with CAD and 162 without it.

A risk score of <−2.9 was 99% predictive for the absence of significant disease; i.e. it was correct in 76 out of 77 cases (Table II). When the threshold of the risk score was lowered to −2.4, the negative predictive value still remained very high (98%; 124 of 127 cases). However, at this level 3 patients with significant CAD also were labelled as having no CAD. A risk score >−0.65 was 59% (16 of 27) sensitive to predict the presence of CAD. This threshold resulted in 6% (9 of 162) of false positive cases. Lowering the threshold to −1.35 increased the sensitivity to 74%, but at the cost of a decrease in specificity to 88%.

Discussion

Patients with severe AR often have a history of chest pain compatible with angina pectoris. Angina may be due to a lower coronary perfusion pressure during diastole and to an increase in wall tension secondary to increased left ventricular volume load.[1,2] Obviously, significant coronary artery narrowing also is one of the main reasons for angina pectoris in these patients. There is wide variation in the reported prevalence of angina and significant CAD in AR.[1-5,10,11] Angina pectoris has been reported from 3%[12] up to 78%.[11] In studies reporting consecutive cardiac catheterization cases, similarly as in the present study, the prevalence of angina varied between 26 and 62% (Table III). The prevalence of significant, angiographically proved CAD has been reported to be within a range of 13 and 37%. Of the 11 patients (mean age 48 years) with pure AR reported by Pichard and associates,[13] none had significant coronary narrowing by arteriography. Of the 17 patients (mean age 42 years) studied by Clark et al,[14] 3 (18%) had significant CAD. In the present study the prevalence of angina and significant CAD was 18 and 14%, respectively. The wide variation in these prevalence figures depends on the group of patients studied and on the definitions that were applied. The highest prevalence figures were reported by Richardson et al[11] with patients who had received valve replacement and myocardial revascularization. In most studies the number of patients was rather small.

Some investigators have included atypical chest pain in the angina class.[5] In the present study this symptom was present in 16%. Inclusion of such patients would almost have doubled the prevalence rate of angina pectoris. Some authors have used as criterion for significant CAD a luminal narrowing of 75%[1] whereas another used 60%.[3] However, in most studies 50% was used as threshold to define angiographically significant CAD. There is general agreement that such narrowing significantly disturbs the coronary circulation in these patients when myocardial oxygen demand is increased.

In the present study, the largest on severe AR reported so far, 151 patients (76%) had angiographically complete normal coronary arteries. A minor degree of CAD was present in 47 patients (24%). However, significant coronary artery stenosis (>50%) was found in only 28 (14%). This was very similar to the prevalence rate reported by Graboys and Cohn,[2] but 2.5 times less than the prevalence reported by Hakki et al[4] and Pathak et al.[5] In the latter studies, only patients >40 years were included. The mean age in these studies was 55 ± 8 and 57 ± 6 years, respectively, whereas in the present study it was 51 ± 11.

Age was significantly related to coronary artery narrowing, not only in our bivariate analysis but also in the multivariate analysis. The patients with significant CAD also had more frequently an elevated serum cholesterol, they smoked more and had more often a history of hypertension. When these variables were used in addition to angina, a multivariate risk score could be calculated that significantly increased the power to predict the presence or absence of CAD. In the 127 patients with a risk score <−2 no CAD was present in 124, resulting in a negative predictive value of 98%. The absence of angina had a negative predictive value of 93%. At 74%, the sensitivity of the multivariate risk score also proved to be significantly greater, as opposed to 57% with almost equal specificity (88 versus 89%) for angina pectoris alone.

Clinical implications: There is general agreement that coronary arteriography should be performed in every patient with severe AR and angina pectoris evaluated with cardiac catheterization. However, there is disagreement as to whether coronary arteriography should be performed routinely in patients with no symptoms of angina pectoris. Some advocate this procedure for all patients over the age of 40, or even 30,[4,5] whereas others are opposed to such measures.[2,3,15,16] Our data are in more agreement with the latter. Based on the findings from the present study it may be concluded that coronary arteriography can safely be omitted before valve replacement in many patients (up to 40%) with severe AR who have no symptoms of ischemic heart disease and who lack risk factors known to increase its incidence.

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Relation Between Serum Nifedipine Concentration and Hemodynamic Effects in Nonobstructive Hypertrophic Cardiomyopathy

SANDRO BETOCCHI, MD, ROBERT O. BONOW, MD, RICHARD O. CANNON, III, MD, LAWRENCE J. LESKO, PhD, HAROLD G. OSTROW, MS, RITA M. WATSON, MD, and DOUGLAS R. ROSING, MD

The relation between nifedipine concentration and hemodynamic effects after sublingual administration of 10 or 20 mg was examined in 13 patients with nonobstructive hypertrophic cardiomyopathy (HC). Serum nifedipine concentrations were determined by gas chromatography and were not related to dose. Peripheral vascular resistance decreased as a function of nifedipine concentration ($r = -0.63$, $p < 0.001$); this was associated with a concentration-related increase in heart rate ($r = 0.56$, $p < 0.001$) and in cardiac index ($r = 0.50$, $p < 0.001$). However, evidence for a pure vasodilator effect of nifedipine was inconsistent, in that the change in stroke volume index with nifedipine was not significant. Although stroke volume index increased at nifedipine concentrations between 60 and 120 ng/ml (38 ± 6 to 42 ± 4 ml/m^2, $p < 0.01$), it decreased at concentrations >120 ng/ml (40 ± 3 to 38 ± 4 ml/m^2, $p < 0.01$). Moreover, pulmonary artery wedge pressure increased at nifedipine concentrations >120 ng/ml (11 ± 2 to 16 ± 4 mm Hg, $p < 0.001$), suggesting either depressed left ventricular (LV) systolic function or reduced LV filling. To investigate these possible mechanisms, LV systolic and diastolic function was studied during catheterization with a nonimaging scintillation probe in 6 of the 13 patients. In these subjects, heart rate was held constant by atrial pacing. Nifedipine, at concentrations ≤120 ng/ml did not alter end-diastolic volume, but increased LV stroke volume and ejection fraction; concentrations >120 ng/ml were associated with increased end-diastolic and end-systolic volumes, reduced ejection fraction and end-systolic pressure-volume ratio. No beneficial effects on LV diastolic function were observed at these higher concentrations, as the time constant of isovolumic relaxation increased (32 ± 13 to 60 ± 11 ms, $p < 0.01$). These results indicate that the hemodynamic effects of nifedipine are related closely to nifedipine concentration in patients with nonobstructive HC. Peripheral vasodilating effects are evident over a wide range of nifedipine levels. At low and medium concentrations, these effects result in augmentation of LV ejection performance; however, negative inotropic effects predominate at high concentrations.

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Verapamil therapy is effective in many symptomatic patients with hypertrophic cardiomyopathy (HC).[1–4] Intravenous verapamil reduces left ventricular (LV) outflow tract gradients[2] and both intravenous and oral verapamil enhance LV relaxation and diastolic filling.[5–10] Nifedipine has also been studied in patients with HC and has been shown to enhance LV relaxation and filling.[11,12] However, such effects have not been observed consistently.[13] In addition, the potent peripheral vasodilating effects of nifedipine may increase outflow gradients in patients with obstructive HC,[13] resulting in net deleterious, rather than advantageous, hemodynamic effects. This compounding influence of increased outflow gradients with nifedipine treatment would not be encountered in patients with nonobstructive HC.

Previous data obtained in patients with coronary artery disease and in normal subjects indicate that a given dose of nifedipine is associated with a wide variability in patient responses[14] and in nifedipine plasma concentrations.[15] The relation between plasma concentration and hemodynamic effects of nifedipine has not been investigated in patients with nonobstructive HC. In the current study we hypothesized that differ-

ent concentrations of the drug might explain the otherwise discordant hemodynamic results of previous studies.

Methods

Patient selection: Thirteen patients with nonobstructive HC participated in this study. There were 7 men and 6 women, ages 18 to 67 years (mean 39). The diagnosis of HC was based on M-mode and 2-dimensional echocardiographic demonstration of a hypertrophied nondilated left ventricle in the absence of another cardiac or systemic disease capable of causing LV hypertrophy.[16] No patient had concomitant coronary artery disease. All patients were symptomatic; 4 were in New York Heart Association functional class II, 8 were in functional class III and 1 was in functional class IV.

After admission, all cardiac medications were discontinued for at least 5 drug half-lives before cardiac catheterization. Each patient gave informed consent before participation in the study according to a protocol approved by the Institutional Clinical Research Subpanel of the National Heart, Lung, and Blood Institute.

Hemodynamic measurements: Patients underwent diagnostic right- and left-sided heart catheterization. A Swan-Ganz thermodilution catheter (Edwards Laboratories, Inc.) was used to measure right heart pressures and cardiac output. For each cardiac output determination at least 3 measurements were averaged. LV pressure was measured with a micromanometer catheter (Millar Instruments, Inc.) in 7 patients, or through a fluid-filled pig-tail catheter (end-hole only, no side holes) in the remaining patients, using the retrograde femoral technique. Systemic blood pressure was monitored by means of a brachial artery catheter. Any patient with an LV outflow gradient >30 mm Hg under resting conditions was excluded from this study. However, patients with provocable outflow gradients (by Valsalva maneuver, amyl nitrite inhalation or isoproterenol infusion) were not excluded.

Control studies included measurements of heart rate, LV pressure, brachial artery pressure, pulmonary wedge pressure and cardiac output. From these determinations, cardiac index, stroke volume index and peripheral vascular resistance index were derived.

Radionuclide measurements: In 6 patients studied with micromanometer catheters, relative changes in LV volume were investigated using an electrocardiographic-gated nonimaging scintillation probe after in vivo labeling of red blood cells with 15 to 20 mCi of technetium-99m. The technical characteristics of the probe and the methodology of data acquisition for these studies have been described in detail elsewhere.[6,13,17] From these data, we constructed LV time activity curves, representing the relation between LV volume and time during the average cardiac cycle. On each curve we computed ejection fraction, peak filling rate and time to peak filling rate.[8] Peak filling rate was measured in counts per second, normalized for the number of counts at end-diastole and expressed as end-diastolic volume/second. Time to peak filling rate was measured relative to end-systole. In addition to these primary measurements, during sequential radionuclide data acquisitions after nifedipine, we measured the percent change in end-diastolic volume and end-systolic volume relative to control end-diastolic counts. These latter measurements were also used to assess the directional changes after nifedipine in the end-diastolic and the end-systolic pressure-volume relations. LV relaxation was assessed by digitizing the LV pressure curve and computing the time constant (T) of the decrease in LV pressure, as previously described.[6,13] Biexponential fitting was also used in all patients and T1 (time constant of LV pressure decrease during the first 40 ms after peak negative dP/dt) and T2 (relative to the second 40 ms) were measured.

It was anticipated that nifedipine administration would increase heart rate, thereby complicating the interpretation of the radionuclide data after nifedipine. We therefore obtained control radionuclide measurements under basal conditions and during sequential atrial pacing at heart rates 10 to 30 beats/min faster than the baseline heart rate in order to facilitate interpretation of the subsequent nifedipine data.

Nifedipine administration: After control data were obtained, nifedipine was administered sublingually. Patients were instructed to break the nifedipine capsule(s) in their mouths and not swallow for several minutes. Nine patients received 20 mg of nifedipine initially, while 4 patients received 10 mg. The initial nifedipine dose was determined individually on the basis of the patient's blood pressure, heart rate and intracardiac pressures. Hemodynamic measurements were repeated at 10, 20 and 30 minutes after administration. A second dose of 10 mg was given to all but 1 patient, and hemodynamic parameters were determined every 10 minutes for the next 30 minutes. In 1 patient the second dose was not administered because his systolic blood pressure decreased below 100 mm Hg after the initial dose of 10 mg of nifedipine. In 6 patients studied simultaneously with the nonimaging scintillation probe, repeat radionuclide measurements were obtained 20 minutes after each dose of nifedipine.

Nifedipine concentration assay: Blood samples were obtained at the time of each hemodynamic measurement. The samples were collected in glass tubes wrapped in aluminum foil, placed on ice and centri-

From the Cardiology Branch, National Heart, Lung, and Blood Institute, and the Computer Systems Laboratory, Division of Computer Research and Technology, National Institutes of Health, Bethesda, and Clinical Pharmacokinetics Laboratory, University of Maryland School of Pharmacy, Baltimore, Maryland. Dr. Betocchi was a recipient of a Fogarty International Research Fellowship F05 TW03350, National Institutes of Health; his present address is Cardiologia I, 2a Facolta di Medicina, Via S. Pansini, 5; 80131 Naples, Italy. Manuscript received August 27, 1987; revised manuscript received December 7, 1987, and accepted December 8.

Address for reprints: Robert O. Bonow, MD, Building 10, Room 7B-15, National Institutes of Health, Bethesda, Maryland 20892.

TABLE I Nifedipine Concentration Values

	Time After Nifedipine Administration (min)					
	10	20	30	40	50	60
Mean + 1 SD (ng/ml)	32 ± 17*	82 ± 55	116 ± 77	79 ± 38	99 ± 47	101 ± 42
Range (ng/ml)	5–61	20–194	25–286	33–141	48–165	50–157

* Value significantly lower ($p < 0.05$) than all subsequent values.
SD = standard deviation.

TABLE II Hemodynamic Effects of Nifedipine

	Nifedipine Concentration								
	Low (≤60 ng/ml)			Medium (61 to 120 ng/ml)			High (>120 ng/ml)		
	C	N	p	C	N	p	C	N	p
Heart rate (beats/min)	81 ± 15	85 ± 16	<0.05	78 ± 15	85 ± 13	<0.05	67 ± 6	86 ± 13	<0.001
Mean blood pressure (mm Hg)	95 ± 14	86 ± 18	<0.01	89 ± 6	79 ± 12	<0.001	91 ± 9	78 ± 7	<0.001
Cardiac index (liters/min/m²)	3.0 ± 0.7	3.2 ± 0.8	<0.01	2.9 ± 0.5	3.5 ± 6	<0.001	2.6 ± 0.3	3.4 ± 0.6	<0.001
Stroke volume index (ml/m²)	37 ± 9	38 ± 9	NS	38 ± 6	42 ± 4	<0.01	40 ± 3	38 ± 3	<0.01
Pulmonary artery wedge pressure (mm Hg)	10 ± 4	10 ± 5	NS	13 ± 5	12 ± 4	NS	11 ± 2	16 ± 4	<0.001
Peripheral vascular resistance (units)	20 ± 5	17 ± 5	<0.001	18 ± 4	14 ± 3	<0.001	20 ± 3	13 ± 3	<0.001

C = control; N = nifedipine; NS = difference not significant.

fuged at the end of the study. The plasma was collected by aspiration and frozen at −20°C until assayed for nifedipine. All sample handling was performed while protecting the specimens from light because of the known instability of nifedipine in plasma exposed to light. Plasma nifedipine concentrations were measured by gas liquid chromatography with electron capture detection.[18] This assay is specific for nifedipine and has a sensitivity of 10 ng/ml with an intra- and interday variation of <12%.

Data analysis: The difference among mean values of nifedipine concentration in the study was tested by means of Duncan's multiple range test.[19] The Student's *t* test for unpaired samples[19] was used to determine whether different doses were associated with different concentrations. To assess the nifedipine concentration-effect relation we used linear regression analysis.[19]

To assess whether an "optimal" nifedipine concentration could be identified nifedipine concentrations were arbitrarily divided as follows: low (≤60 ng/ml), medium (61 to 120 ng/ml) and high (>120 ng/ml) nifedipine concentrations. Hemodynamic parameters measured in each concentration range were compared to the corresponding control value by the paired *t* test.[19] All measurements are expressed as the mean ± 1 standard deviation.

Results

Nifedipine concentration: Figure 1 shows the time course of nifedipine concentration in patients receiving 10 or 20 mg as a first dose. No differences were observed between nifedipine concentration values measured in patients receiving 20 mg and 10 mg at any time during the study. Mean values of nifedipine concentration, independent of initial dosing, increased over the first 20 minutes, then plateaued (Table I). A high (>120 ng/ml) nifedipine concentration was reached in 5 patients (17 observations).

Hemodynamic data: Nifedipine administration resulted in a significant decrease in peripheral vascular resistance and increase in heart rate and cardiac index (Table II), and the magnitude of changes in these variables correlated significantly with plasma drug level. The percent change in peripheral vascular resistance index decreased ($r = 0.63$, $p < 0.001$) as a function of nifedipine concentration (Figure 2), and the percentage change in heart rate and cardiac index increased with increasing drug concentrations ($r = 0.56$ and 0.50, $p < 0.001$ for both).

In contrast, stroke volume index had directional changes dependent on nifedipine concentration (Figure 3); it increased 17% (38 ± 6 to 42 ± 4 ml/m², $p < 0.01$) with nifedipine concentrations between 60 and 120 ng/ml, but decreased relative to control by 5% (40 ± 3 to 38 ± 4 ml/m², $p < 0.01$) at concentrations >120 ng/ml. The change in mean pulmonary artery wedge pressure correlated with nifedipine concentration ($r = 0.56$, $p < 0.001$), and a significant increase in pulmonary wedge pressure was observed at high nifedipine concentrations (Table II and Figure 4). Only 2 patients had an abnormal (>15 mm Hg) pulmonary artery

wedge pressure at baseline; therefore, no attempts were made to analyze separately the effects of nifedipine in patients with normal versus elevated pulmonary artery wedge pressures. No patient developed an LV outflow tract gradient ≥30 mm Hg during nifedipine administration.

Radionuclide data: We assessed the influence of nifedipine concentration on LV systolic and diastolic function by analyzing data obtained at high (>120 ng/ml) and low or medium nifedipine concentrations (≤120 ng/ml). The lower nifedipine concentration group consisted of 6 determinations, whereas the high concentration group was made up of 5 radionuclide studies. Mean nifedipine concentrations were 68 ± 36 and 172 ± 14 ng/ml, respectively. These results are listed in Table III. At low and medium nifedipine concentration, end-diastolic volume did not change, whereas end-systolic volume decreased significantly. As a consequence, ejection fraction increased. Peak filling rate increased and time to peak filling rate shortened significantly. In contrast, the time constant of isovolumic relaxation did not improve, and its late component (T2) was significantly slowed. At high nifedipine concentration a significant increase in both end-diastolic and end-systolic volumes was observed, associated with a decrease in ejection fraction. The end-systolic pressure volume ratio also decreased significantly, with a shift downward and rightward in the end-systolic pressure-volume relation. The elevated end-diastolic volume was associated with increased end-diastolic pressure. Isovolumic relaxation was impaired as both the time constant T and its late component T2 increased at high nifedipine concentrations.

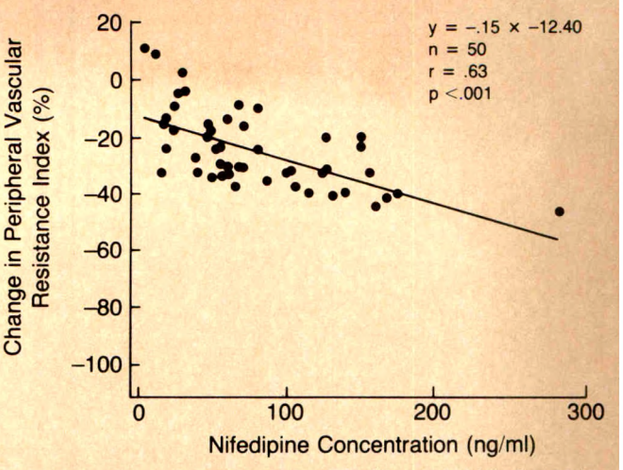

FIGURE 2. Percentage change of the index of peripheral vascular resistance plotted as a function of nifedipine concentration.

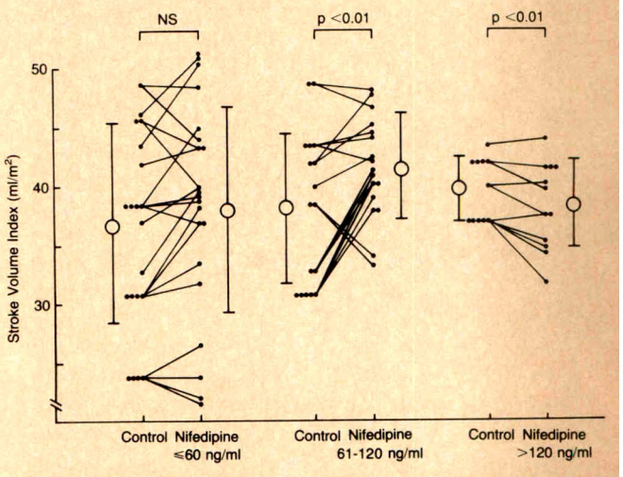

FIGURE 3. Influence of low (*left*), medium (*middle*) and high nifedipine concentrations (*right*) on left ventricular stroke volume index. *Open circles* with vertical bars represent mean values ± 1 standard deviation.

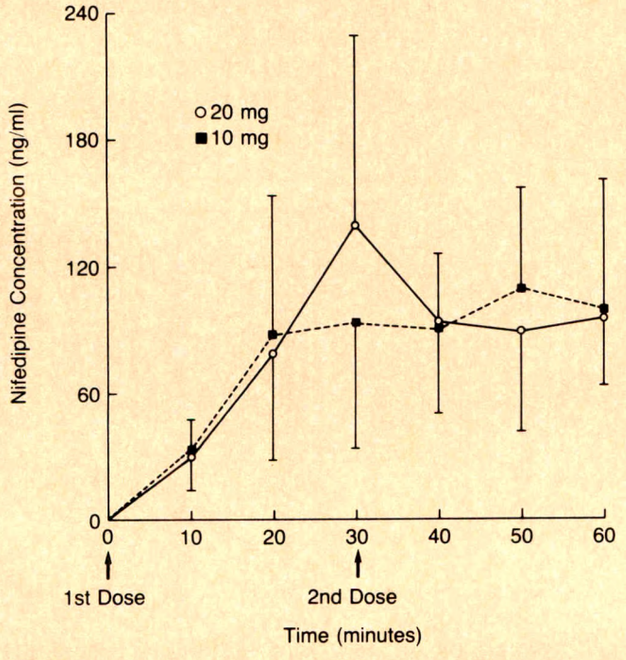

FIGURE 1. Time course of mean nifedipine concentrations in patients receiving 20 mg (*solid lines*) or 10 mg (*dashed lines*) as their first dose. No significant difference was observed between the 2 groups of patients at any point.

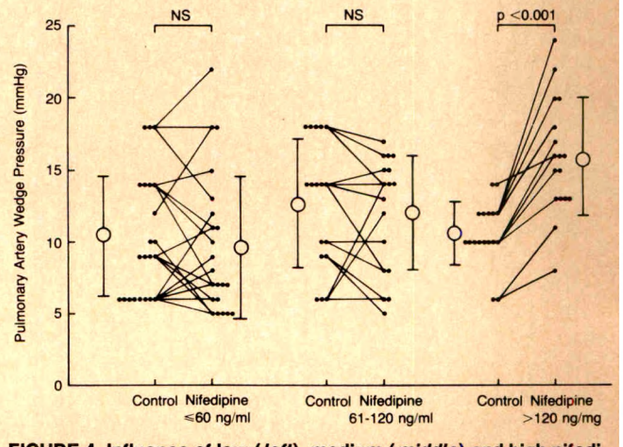

FIGURE 4. Influence of low (*left*), medium (*middle*) and high nifedipine concentrations (*right*) on pulmonary artery wedge pressure. *Open circles* with vertical bars represent mean values ± 1 standard deviation.

TABLE III Effects of Nifedipine Concentration on Radionuclide Measurements

	Nifedipine Concentration					
	Low or medium (≤120 ng/ml)			High (>120 ng/ml)		
	C	N	p	C	N	p
Heart rate (beats/min)	88 ± 23	87 ± 22	NS	83 ± 10	88 ± 14	NS
LV end-diastolic volume (% of control)	100	94 ± 14	NS	100	152 ± 30	<0.01
LV end-systolic volume (% of control EDV)	41 ± 8	28 ± 17	<0.05	21 ± 16	52 ± 33	<0.01
LV ejection fraction (%)	59 ± 8	72 ± 17	<0.01	79 ± 17	68 ± 15	<0.05
LV end-systolic pressure-volume ratio	3 ± 0.2	15 ± 24	NS	12 ± 11	3 ± 2	<0.05
Peak LV filling rate (EDV/s)	3.7 ± 1.2	4.7 ± 1.6	<0.01	5.4 ± 1.0	4.8 ± 1.9	NS
Time to peak filling rate (ms)	230 ± 29	194 ± 43	<0.01	261 ± 67	228 ± 112	NS
Time constant of LV relaxation (ms): T	38 ± 7	46 ± 10	NS	42 ± 14	56 ± 12	<0.01
T1	46 ± 1	47 ± 10	NS	56 ± 14	56 ± 17	NS
T2	34 ± 11	47 ± 15	<0.01	32 ± 13	60 ± 11	<0.01
Nifedipine concentration (ng/ml)		68 ± 36			172 ± 14	

C = control; EDV = end-diastolic volume; LV = left ventricular; N = nifedipine; NS = difference not significant.

An improvement in the diastolic pressure-counts relation (as assessed by downward-rightward shift of the diastolic portion of the curve) was observed in only 1 patient at high and in 1 patient at low nifedipine concentrations. In this latter patient at a nifedipine concentration of 20 ng/ml, a consistent improvement of peak filling rate and shortening of time to peak filling rate was observed.

Discussion

Nifedipine concentration: Nifedipine concentration increased over the first 20 minutes after its sublingual administration, but then plateaued for the remainder of the study (Table I). There was a wide range of concentrations achieved for a given dose, and the mean blood levels did not differ between those patients who received 10 mg as their initial dose and those who received 20 mg (Figure 1). These results correspond to observations made during previous investigations, using sublingual,[20,21] intravenous[15,21] or oral administration[15,21] of nifedipine.

Relation between nifedipine concentration and hemodynamic effect: In our patients with nonobstructive HC, the anticipated decrease in peripheral vascular resistance after nifedipine administration was linearly related to drug concentration (Figure 2), as was the reflex increase in heart rate. A similar concentration-dependent decrease in peripheral vascular resistance has already been demonstrated in dogs[22] and in hypertensive patients.[20,23,24] Evidence against a pure peripheral vasodilating effect, however, was apparent in the stroke volume response to nifedipine (Figure 3); although stroke volume index increased significantly at low and medium range nifedipine concentrations (60 to 120 ng/ml) it decreased significantly at high concentrations (>120 ng/ml). In addition, mean pulmonary artery wedge pressure increased at high nifedipine concentrations (Figure 4).

The differential effects on stroke volume index, as well as our radionuclide data, suggest that 2 distinctly opposite hemodynamic patterns result at different plasma concentrations of nifedipine. At low or medium nifedipine concentration the increase in stroke volume can be explained by the radionuclide data: end-systolic volume decreased whereas end-diastolic volume was unchanged. Therefore, ejection fraction increased. This is probably due to afterload reduction rather than to increased contractility, as the end-systolic pressure-volume ratio did not change. The end-diastolic pressure-volume relation was also not altered.

In this concentration range, an increase in peak filling rate and a shortening in time to peak filling rate were observed. In the absence of changes in the time constant of LV relaxation or in LV distensibility characteristics, we interpret the increase in peak filling rate as purely a reflection of augmented ejection fraction.

In contrast, a negative inotropic effect was observed at high nifedipine concentration, as shown by the decreases in ejection fraction in stroke volume index, and in the end-systolic pressure-volume ratio. This response at high drug concentrations may be explained by the primary effect of nifedipine to reduce contractility,[25] which in the intact animal and in man is usually counterbalanced by marked afterload reduction and a reflex increase in sympathetic activity.[20] At elevated nifedipine blood levels, however, the primary negative inotropic effect becomes clinically evident. At these high concentrations, LV compliance was unchanged such that the increased LV end-diastolic volume was associated with elevated LV end-diastolic and pulmonary artery wedge pressures.

These data suggest that high nifedipine blood levels may be potentially detrimental in patients with HC, as the negative inotropic effect is associated with reduced stroke volume and increased pulmonary artery wedge pressure without demonstrable effects on LV diastolic function. In contrast, "optimal" nifedipine concentrations seem to be those ≤120 ng/ml. The practical applications of these observations are limited, as a given dose of nifedipine is associated with totally unpredictable blood levels, as observed in this and other studies[20,21] with sublingual administration, and in previous investigations using oral or intravenous administra-

tion.[14,21] These unpredictable results necessitate caution in the use of nifedipine in patients with nonobstructive HC.

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A Comparative Study of Thallium-201 Single-Photon Emission Computed Tomography and Electrocardiography in Duchenne and Other Types of Muscular Dystrophy

SHUHEI YAMAMOTO, MD, HIDEO MATSUSHIMA, MD, AKIO SUZUKI, MD, IWAO SOTOBATA, MD, TOSHIKATSU INDO, MD, and YUKIHIKO MATSUOKA, MD

Single-photon emission computed tomography (SPECT) using thallium-201 was compared with 12-lead electrocardiography (ECG) in patients with Duchenne (29), facioscapulohumeral (7), limb-girdle (6) and myotonic (5) dystrophies, by dividing the left ventricular (LV) wall into 5 segments. SPECT showed thallium defects (37 patients, mostly in the posteroapical wall), malrotation (23), apical aneurysm (5) and dilatation (7). ECG showed abnormal QRS (36 patients), particularly as a posterolateral pattern (13). Both methods of assessment were normal in only 7 patients. The Duchenne type frequently showed both a thallium defect (particularly in the posteroapical wall) and an abnormal QRS (predominantly in the posterolateral wall); the 3 other types showed abnormalities over the 5 LV wall segments in both tests. The percent of agreement between the 2 tests was 64, 66, 70, 72 and 72 for the lateral, apical, anteroseptal, posterior and inferior walls, respectively. The 2 tests were discordant in 31% of the LV wall, with SPECT (+) but ECG (−) in 21% (mostly in the apicoinferior wall) and SPECT (−) but ECG (+) in 10% (mostly in the lateral wall). Some patients showed large SPECT hypoperfusion despite minimal electrocardiographic changes. ECG thus appeared to underestimate LV fibrosis and to reflect posteroapical rather than posterolateral dystrophy in its posterolateral QRS pattern. In this disease, extensive SPECT hypoperfusion was also shown, irrespective of clinical subtype and skeletal involvement.

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In the clinically advanced stage of muscular dystrophy, left ventricular (LV) involvement (myocardial dystrophy) is inevitable and the electrocardiograms are often abnormal.[1-5] In addition, a specific electrocardiographic pattern is observed in X-linked muscular dystrophy of the Duchenne type, i.e., anteromedial shift of the QRS wave.[3,4] Among several hypotheses proposed for its pathogenesis,[1-7] that of posterolateral wall fibrosis is widely accepted, being also supported by data from methodologies other than electrocardiography (ECG).[3,4,6,7] However, few papers have reported the sensitivity of ECG in assessing myocardial dystrophy. Thus, ECG seems to have been accepted a priori as a satisfactory method to screen LV involvement in this disease. Although LV myocardial infarction has been evaluated via single-photon emission computed tomography (SPECT) with thallium-201,[8,9] there have been no reports, to our knowledge, of the application of SPECT to the evaluation of a large series of patients with muscular dystrophy. Therefore, we studied 47 patients with several types of muscular dystrophy by SPECT, regardless of their ECG findings.

This study addressed the following questions: (1) What are the characteristics of the SPECT image in each type of muscular dystrophy? (2) How does SPECT correlate with ECG? More specifically, do patients with the typical posterolateral electrocardiographic

From the First Department of Internal Medicine and Department of Neurology, Nagoya University School of Medicine, Nagoya, Japan. Manuscript received August 28, 1987; revised manuscript received December 3, 1987, and accepted December 4.

Address for reprints: Shuhei Yamamoto, MD, Department of Pharmacology and Therapeutics, School of Medicine and Dentistry, State University of New York at Buffalo, 127 Farber Hall, Buffalo, New York 14214.

pattern show SPECT hypoperfusion confined to that wall? (3) How do these results correlate with skeletal involvement? Does the latter predict the former?

Methods

Patient selection: The entry criterion for this study was a firm diagnosis of muscular dystrophy with either Duchenne, myotonic, limb-girdle or facioscapulohumeral type, based on clinical characteristics, serum creatine kinase levels, electromyograms and muscle biopsy. The exclusion criteria included previous heart surgery or the presence of congenital or valvular heart disease, other systemic diseases in addition to muscular dystrophy, use of drugs that would affect the electrocardiogram, LV or right ventricular hypertrophy, complete bundle branch block or fascicular block on the electrocardiogram. Forty-seven patients were randomly selected from our clinic: 43 men and 4 women (ages 9 to 62 years) with Duchenne (29 patients), facioscapulohumeral (7), myotonic (6) or limb-girdle (5) type. Informed written consent was obtained from each patient before the study. SPECT and ECG were performed on the same day.

Single-photon emission computed tomography: Five minutes after intravenous injection of thallium-201 (2 mCi), SPECT was performed, using a Toshiba GCA-70-TOKU gamma camera and a Toshiba GMS-55A computer. The camera consisted of dual-headed detectors (35 × 50 cm^2) equipped with low-energy, all purpose, parallel-hole collimators with a spatial resolution of 17 mm (full width half maximum), as described elsewhere.[10] Briefly, data were acquired with 128/128 matrix format by 6° sampling steps and 20-second imaging time over the 360° arc in 10 minutes. Then trans-, long- and short-axial tomograms (3, 3 and 6, respectively) were reconstructed on a 16-mm width slice by a filtered back projection algorithm (Shepp & Logan filter), photon attenuation correction (Chang), spatial smoothing and background processing (Goris).

Left ventricular fibrosis: In each image we assessed the anteroseptal, apical, lateral, posterior and inferior LV walls by circumferential profile analysis,[11] using 15 healthy men as volunteers. We defined LV walls with subnormal profile counts (mean − 2 standard deviations) as hypoperfused.

Morphology: The LV boundary was defined as 50% of the maximal count with a region of interest drawn around each LV image.

Regarding malrotation (Figure 1), 2 angles were identified: 1 between the LV axis and the sagittal plane projected on the transaxial image and 1 between the former and the horizontal plane. By comparison with data from 108 normal adults (mean ± 2 standard deviations) obtained by the same method, the LV axis was assumed to be oriented counterclockwise or clockwise if the former angle was <20° or >55°, respectively, and horizontally or vertically if the latter angle was <20° or >65°, respectively.

In hypertrophy and dilatation, the LV cavity to LV wall ratio was obtained (short-axial images). LV wall was then defined as hypertrophic, normal, dilated or ballooning if the ratio was <0.5, 0.5 to 1.0, 1.1 to 2.0, or >2.0, respectively. The right ventricle was defined as hypertrophic if it was clearly visualized in the transaxial image.

An LV aneurysm was assumed to be present if the LV cavity widened toward a particular wall.

Standard 12-lead electrocardiography: The morphology and amplitudes of the QRS wave were determined in each electrocardiographic lead. Based on normal data from children and adults,[12–14] electrocardiographic criteria for each LV wall lesion were as follows (QRS criteria, suspected wall): (1) abnormally deep Q or decreased R in leads V_1, V_2 and V_3 (anterior wall, i.e., anteroseptal and apical walls combined); (2) decreased R in leads V_5 and V_6 or abnormally deep Q in leads V_5, V_6, I, aVL (lateral wall); (3) tall R or increased R/S ratio in leads V_1 and V_2 (posterior wall); and (4) abnormal Q in leads II, III, aVF (inferior wall). The combination of (2) and (3) was defined as the "distinctive" electrocardiographic pattern.[3] Rhythm disturbances, repolarization abnormalities, electrical axis deviation and ventricular or supraventricular premature activities were also assessed.

Musculoskeletal involvement (clinical stage): A gradation from mildest (1) to severest (8) was used on the basis of a detailed clinical examination.[15]

Statistics: In SPECT versus ECG, the incidences of SPECT hypoperfusion and abnormal QRS were compared in each LV wall, using Fisher's exact test. In LV malrotation versus ECG, 2 groups, those with and without such malrotations in the SPECT images, were compared for their incidences of abnormal QRS in each LV wall, using Fisher's exact test. In skeletal versus LV involvement, 2 sets of paired data for each patient were examined, the clinical stage versus the number of hypoperfused walls (SPECT) and the clinical stage versus the number of walls with abnormal QRS (ECG), both using Spearman's rank correlation test. A p value of <0.05 was considered significant in all cases.

Results

Table I lists the results and Tables II to IV are its summaries.

Single-photon emission computed tomography: SPECT hypoperfusion was shown in 40% of 235 LV walls and in 79% of the 47 patients. Although hypoper-

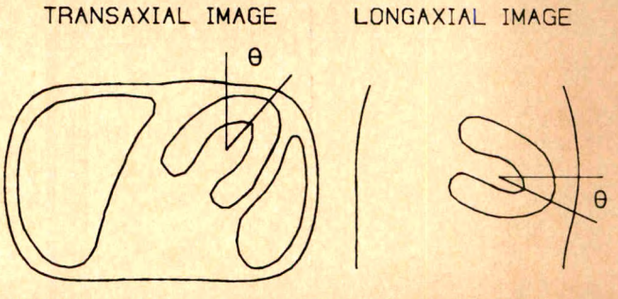

FIGURE 1. Assessment of orientation of the cardiac axis by the angles projected on transaxial (*left*) and long-axial (*right*) images of thallium-201 SPECT.

TABLE I Clinical, Electrocardiographic and Scintigraphic Data of 47 Patients with Four Classic Types of Muscular Dystrophy

Pt	Age (yr), Sex	Type	Clinical Stage	Location of Suspected LV Fibrosis		LV Morphology (SPECT)		
				ECG	SPECT	Dilatation*	Aneurysm	Malrotation
1	9, M	DMD	1	N	N	0	–	–
2	9, M	DMD	5	L, P	P	0	–	–
3	11, M	DMD	2	L	AS, AP	0	–	V
4	11, M	DMD	4	P	P	0	–	CC
5	12, M	DMD	7	P	P	0	–	–
6	13, M	DMD	5	L, P, I	AP, L, P, I	0	–	–
7	13, M	DMD	6	L, P	AS, AP, P, I	+1	–	–
8	14, M	DMD	6	L, P	AS, P	0	–	V
9	15, M	DMD	5	P	AS, P, I	0	–	V
10	16, M	DMD	6	P	AP, L, P	0	–	–
11	16, M	DMD	7	L	AP, L, P, I	0	–	V
12	16, M	DMD	7	L, P	AP	0	+	–
13	16, M	DMD	8	AS, AP, L, P	diffuse	+2	–	–
14	17, M	DMD	6	AS, AP, L	AP, P	0	–	–
15	17, M	DMD	7	P	P	0	–	V
16	17, M	DMD	7	L, P	AS, AP, L, P	+1	–	CC
17	17, M	DMD	7	L, P	AP, L, P	0	–	CC
18	18, M	DMD	6	AS, AP, L	AS, AP, P	0	–	–
19	18, M	DMD	7	AS, AP, L, P	AP, L, P	0	+	V
20	18, M	DMD	8	P	AS, AP, P, I	0	–	H
21	20, M	DMD	5	N	N	0	–	V
22	20, M	DMD	5	N	N	0	–	–
23	20, M	DMD	6	L, P	AP, P	0	–	–
24	20, M	DMD	7	L, P	P	0	–	–
25	20, M	DMD	7	L, P	L, P	0	–	V
26	20, M	DMD	7	N	AS, AP, P	+1	+	–
27	20, M	DMD	8	P	AS, AP, P, I	0	–	–
28	21, M	DMD	6	L, P	AS, AP, P	0	+	V
29	26, M	DMD	7	AS, AP, L	AS, AP, P, I	+1	–	CC
30	23, M	FSH	1	AS, AP	AS, AP, I	+1	–	V
31	30, M	FSH	2	AS, AP	AS, AP, P, I	0	–	–
32	35, M	FSH	1	AS, AP, L	AP, I	0	–	V
33	37, M	FSH	1	N	P	0	–	CC
34	38, M	FSH	3	L	N	0	–	V
35	41, F	FSH	5	L	N	0	–	–
36	62, M	FSH	2	AS, AP, L	AS	0	–	CC
37	34, M	MT	1	L, P	L, P, I	0	–	H, CC
38	35, F	MT	7	N	N	0	–	CC
39	36, M	MT	7	N	N	0	–	–
40	41, M	MT	1	L, P	AP	0	–	H
41	42, M	MT	2	N	P, I	0	–	–
42	47, M	MT	7	P	N	0	–	–
43	25, M	LG	5	L, P	AS, AP, L	0	+	CC
44	39, M	LG	2	N	AS	0	–	–
45	45, M	LG	2	AS, AP	AS, AP, P, I	+2	–	–
46	51, F	LG	2	N	N	0	–	–
47	53, F	LG	2	N	N	0	–	–

* LV dilatation (see Methods): +2 = ballooning; +1 = moderate; 0 = absent.

AP = apical; AS = anteroseptal; CC = counterclockwise rotation; DMD = Duchenne muscular dystrophy; ECG = standard 12-lead electrocardiography; FSH = facioscapulohumeral muscular dystrophy; H = horizontal heart; I = inferior; L = lateral; LG = limb-girdle muscular dystrophy; LV = left ventricle; MT = myotonic dystrophy; N = normal result; P = posterior; SPECT = (thallium-201) single-photon emission computed tomography; V = vertical heart.

fusion was most frequent in the posterior wall, it showed a wide distribution pattern in that 19 different patterns were identified among the 47 patients. SPECT showed LV malrotations in 49% of the patients, including vertical heart (12), counterclockwise rotation (8), horizontal heart (2) and horizontal heart with counterclockwise rotation (1). SPECT also showed LV aneurysm (5), dilatation (5) and ballooning (2), but hypertrophy was not found.

Electrocardiography: Abnormal QRS was shown in 30% of the LV walls and in 77% of the patients. It was most frequent in the lateral wall, followed by the posterior wall. In contrast to SPECT, the electrocardiogram was specific in its pattern. Among the 7 patterns into which the abnormal QRS was classified, that of posterolateral wall injury was the most frequent, being seen in 13 patients. Moreover, 10 of these 13 patients consisted mostly of Duchenne type (patients 2, 7, 8, 12, 16, 17, 23, 24, 25 and 28), whereas the 3 others consisted of myotonic type (patients 37 and 40, siblings) and limb-girdle type (patient 43). ECG showed first degree atrioventricular block (3 patients), ventricular (2) and

TABLE II QRS-Wave Abnormalities (Electrocardiography) and Hypoperfusion (Scintigraphy) Among the Five LV Walls in Each of the Four Clinical Types of Muscular Dystrophy

Clinical Type	Location in LV					Total
	Anteroseptal	Apical	Lateral	Posterior	Inferior	
SPECT						
DMD (n = 29)	12 (41%)	18 (62%)	8 (28%)	24 (83%)	8 (28%)	70 (48%)
FSH (n = 7)	3 (43%)	3 (43%)	0 (0%)	2 (29%)	3 (43%)	11 (31%)
MT (n = 6)	0 (0%)	1 (17%)	1 (17%)	2 (33%)	2 (33%)	6 (20%)
LG (n = 5)	3 (60%)	2 (40%)	1 (20%)	1 (20%)	1 (20%)	8 (32%)
Total 47	18 (38)%	24 (51%)	10 (21%)	29 (62%)	14 (30%)	95 (40%)
ECG						
DMD (n = 29)	5 (17%)	5 (17%)	18 (62%)	20 (69%)	1 (3%)	49 (34%)
FSH (n = 7)	4 (57%)	4 (57%)	4 (57%)	0 (0%)	0 (0%)	12 (34%)
MT (n = 6)	0 (0%)	0 (0%)	2 (40%)	3 (50%)	0 (0%)	5 (17%)
LG (n = 5)	1 (20%)	1 (20%)	1 (20%)	1 (20%)	0 (0%)	4 (16%)
Total 47	10 (21%)	10 (21%)	25 (53%)	24 (51%)	1 (2%)	70 (30%)

Abbreviations as in Table I.

TABLE III Classification of Patients with Four Clinical Types of Muscular Dystrophy by LV Involvement Patterns in Scintigraphy or Electrocardiography

SPECT/ECG Pattern						Clinical Type				
	Site of Involvement									
Pattern*	AS	AP	L	P	I	DMD (n = 29)	FSH (n = 7)	MT (n = 6)	LG (n = 5)	Total (n = 47)
SPECT										
1	+	+		+	+	4	1		1	6
2				+		5	1			6
3	+	+		+		3				3
4		+	+	+		3				3
5		+	+	+	+	2				2
6		+		+		2				2
7	+						1		1	2
8		+				1		1		2
9	+	+	+	+	+	1				1
10	+	+	+	+		1				1
11	+	+	+						1	1
12	+	+			+		1			1
13	+			+	+	1				1
14			+	+	+			1		1
15	+	+				1				1
16		+		+		1				1
17			+	+		1				1
18				+	+			1		1
19		+			+		1			1
Normal perfusion						3	2	3	2	10
ECG										
1			+	+		10		2	1	13
2				+		7		1		8
3	+	+	+			3	2			5
4			+			2	2			4
5	+	+					2		1	3
6	+	+	+	+		2				2
7			+	+	+	1				1
Normal QRS waves						4	1	3	3	11

* SPECT and ECG were classified into 19 and 7 distinctive patterns, respectively (see text).

Abbreviations as in Table I. In the columns for SPECT and ECG patterns, + denotes the presence of thallium hypoperfusion and QRS-wave abnormalities in each LV wall, respectively (see Methods).

supraventricular (4) premature beats, and abnormal right (1) and left (4) axis deviations. Changes in ST segment were also shown (15 patients), but the marked convex precordial ST elevation suggestive of anterior aneurysm was not seen.

Correlation between SPECT and ECG: Only 7 of the 47 patients showed normal SPECT and ECG results. Of the 40 others, 7 exhibited conflicting results, with no SPECT hypoperfusion despite abnormal QRS in 3 and vice versa in 4. In addition, 1 of the latter 4

TABLE IV Relation Between Scintigraphy and Electrocardiography in Terms of LV Wall Involvement in Each of the Five LV Walls

		Location in LV					
SPECT*	ECG†	Anteroseptal	Apical	Lateral	Posterior	Inferior	Total
+	+	7 (15%)	9 (19%)	9 (19%)	20 (42%)	1 (2%)	46 (20%)
−	−	26 (55%)	22 (47%)	21 (45%)	14 (30%)	33 (70%)	116 (49%)
+	−	11 (23%)	15 (32%)	1 (2%)	9 (19%)	13 (28%)	49 (21%)
−	+	3 (6%)	1 (2%)	16 (34%)	4 (9%)	0 (0%)	24 (10%)
% agreement		70%	66%	64%	72%	72%	69%
p Value		NS	<0.05	<0.05	<0.01	NS	

* + and − denote hypoperfusion and normal perfusion, respectively (see Methods); † + and − denote QRS-wave abnormality and normal QRS waves, respectively (see Methods).
NS = not significant. Other abbreviations as in Table I.

patients showed SPECT hypoperfusion extending over the 3 LV segments despite only mild ST changes in the precordial leads (patient 26). Of the 13 patients with the posterolateral wall pattern, only 1 showed SPECT hypoperfusion confined to that wall (patient 25), whereas 8 showed, with or without lateral wall hypoperfusion, apical hypoperfusion as well (patients 7, 12, 16, 17 23, 28, 40 and 43) and the remaining 4 showed posterior (patients 2 and 24), anteroseptoposterior (patient 8) and posterolateroinferior (patient 37) hypoperfusion.

Among the 4 clinical types, the Duchenne type was most frequently characterized by both SPECT and ECG abnormalities. This group showed abnormal QRS complexes predominantly in the posterior and lateral walls as the distinctive ECG pattern, with

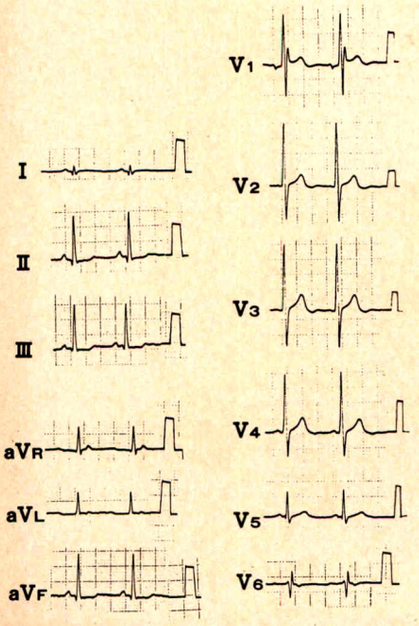

FIGURE 2. Standard 12-lead electrocardiogram (patient 28) shows posterolateral wall pattern, i.e., increased R (≥1.0 mV) and R/S ratio (≥1.0) in V_1 and V_2 and diminished R (≤1.0 mV) in V_5 and V_6. All calibrations are 1.0 mV.

SPECT hypoperfusion most frequently seen in the posterior wall, followed by the apical wall and occasionally the lateral wall. In the non-Duchenne types, SPECT and QRS abnormalities were both scattered over the 5 LV segments. The overall combined results of SPECT hypoperfusion and abnormal QRS in the 5 LV walls were (−) in 49% and (+) in 20% (Table IV), which gave an overall agreement of 69%. The percent agreement in each wall ranged from 64 to 72%. In the apical, lateral and posterior walls, the incidence of SPECT hypoperfusion correlated significantly with that of abnormal QRS. The 2 tests were discordant in 31% of LV walls, with SPECT (+) but ECG (−) in 21%, particularly in the apical wall, and vice versa in 10%, especially in the lateral wall. The anteroseptal and inferior walls did not show correlation between the SPECT and ECG results. The complication of LV malrotation did not influence the abnormal QRS, meaning that in no wall did the percent agreement of SPECT with ECG show significant difference between patients with and without LV malrotation (23 and 24 patients, respectively). None of the electrocardiographic findings except abnormal QRS was indicative of the distribution of SPECT hypoperfusion.

Systemic versus left ventricular involvement: The number of walls with SPECT hypoperfusion or with abnormal QRS complexes was 2.02 ± 1.51 or 1.49 ± 1.12, respectively (mean ± standard deviation). Neither result showed significant correlation with the clinical stage, which ranged from mildest (grade 1) to severest (grade 8) (4.85 ± 2.39, mean ± standard deviation). Patients 30 and 45 showed slight skeletal involvement (clinical stage <3) despite extensive hypoperfusion and LV dilatation in their SPECT images.

Two case presentations: Patient 28 (Figures 2 and 3) had had no symptoms of LV failure and had taken no cardiovascular drugs. His electrocardiogram was suggestive of a posterolateral lesion. In contrast, his SPECT showed posterior and anteroapical lesions—the latter being larger and evolving into an aneurysm—plus vertical heart status. The lateral wall showed normal perfusion. These SPECT results were confirmed by tomographic echocardiography as posterior and apical wall dyskinesia and vertical orientation of the anatomical LV axis. Thus, the posterolateral

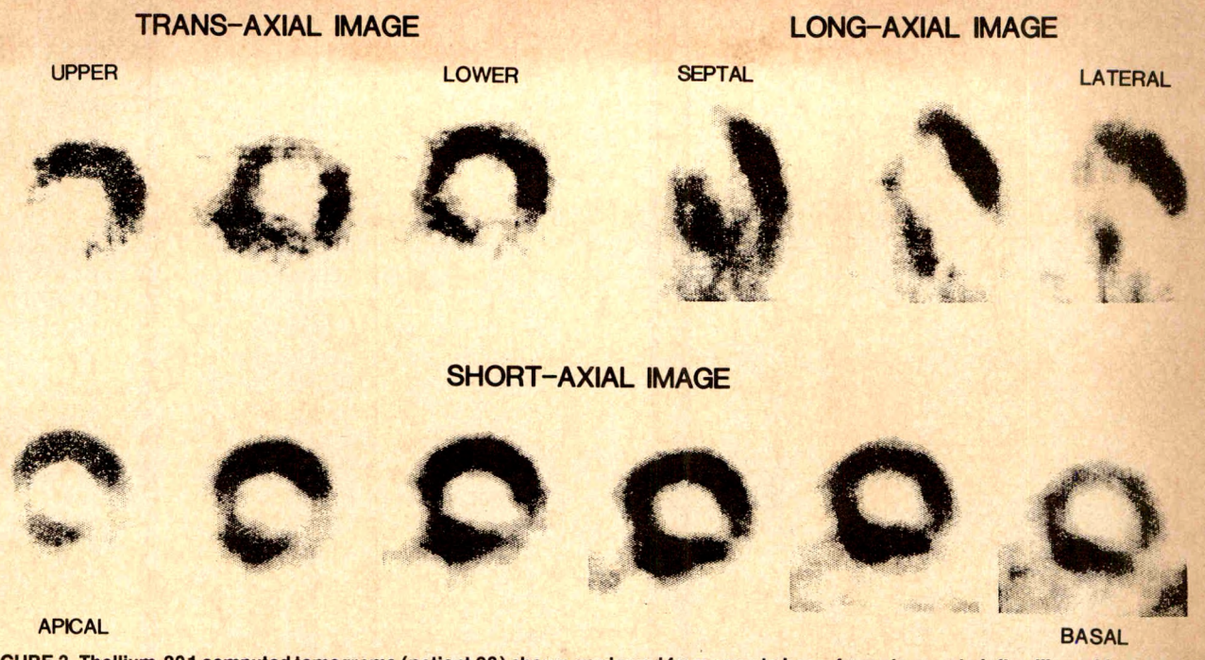

FIGURE 3. Thallium-201 computed tomograms (patient 28) shown as viewed from apex to base, from sternum to left axilla and from apex to base, respectively, in the trans- (3 images in the *left upper row*), long- (3 images in the *right upper row*) and short-axial (6 images in the *lower row*) images. In contrast to the electrocardiogram, the thallium scintigram showed solitary perfusion defect in the anteroapical wall and in the posterior wall (the former was larger than the latter). The LV cavity widened toward the apex. The angle between the LV long axis and the horizontal plane, which is projected on the long-axial image, was 70°. Reproduced with permission from Kaku Igaku.[18]

ECG pattern of the Duchenne type is not necessarily accompanied by SPECT hypoperfusion confined to that wall.

Patient 13 (Figures 4 and 5) had an electrocardiogram suggestive of posterolateral and anterior injuries, but was asymptomatic. His SPECT showed diffuse LV hypoperfusion, LV ballooning and marked lung uptake of thallium. In terms of these SPECT results, his prognosis for survival appeared doubtful. Six months after the study, he developed refractory heart failure and died 2 months thereafter. Thus, it is apparent that ECG may underestimate myocardial dystrophy that is demonstrable by SPECT.

Discussion

With sensitivity of 87% and specificity of 93%,[9] thallium-201 SPECT is an established method of assessing LV infarction. In a canine model, it accurately estimated by circumferential profile analysis the extent of infarcts that weighed from 7 to 40 g.[16] In muscular dystrophy, LV fibrosis has been assessed with various noninvasive methods[1-5,6] because left ventriculography is not justifiable in most patients. Reports on thallium imaging, however, are few.[7,17,18] In our present SPECT study, quantitative diagnosis of LV hypoperfusion as well as gross LV morphology were easily carried out although the diagnosis was also obvious by inspection in most cases.

Pathophysiology of thallium defect in muscular dystrophy: According to recent electron microscopic[19-21] and biochemical[22-25] studies, the plasma membrane is believed to be primarily affected in muscular dystrophy, i.e., before the gross pathologic changes occur. The myocardium may thus show reduced thallium uptake as a result of altered sarcolemmic permeability to the ion, even if the myocardium is structurally normal. In addition, the autopsy of Duchenne types often reveals loss of myocardial cells responsible for thallium uptake.[1-4] Thus, localized loss of the uptake implies severe dystrophy or fibrosis, although SPECT cannot diagnose a diffuse lesion or a small lesion beyond its spatial resolution. Thallium hypoperfusion was reportedly seen in 27% of boys with Duchenne dystrophy in planar imaging.[7] In contrast, our SPECT study showed hypoperfusion in 90% of Duchenne boys and in 61% of the 3 other types combined. It is known that, because of photon attenuation, the diagnostic reliability of planar imaging in LV infarction is lowest in the posteroinferior wall,[9] where dystrophy is likely to be most frequent. More importantly, SPECT is relatively free of unwanted contributions from overlapping tissues. Because SPECT is thought to detect multiple dystrophic lesions difficult to assess with planar imaging, we believe our study was valid in demonstrating frequent LV involvement in muscular dystrophy, as shown by reduced thallium uptake. The SPECT image also frequently demonstrated concurrent abnormal LV morphology (dilatation and aneurysm) and LV malrotations accompanying chest deformities.

Pathogenesis of abnormal QRS in muscular dystrophy: Several mechanisms have been proposed for the abnormal QRS: (1) reduced electromotive forces due to LV fibrosis,[1-4] (2) chest deformity,[1] (3) right ven-

tricular or septal hypertrophy,[1-2] (4) coexisting coronary artery disease,[26] (5) chest muscle atrophy,[1] (6) genetic predilection[5] and (7) impaired electrical conduction.[27] Our study basically supports hypothesis (1) because the results of our ECGs and SPECTs agreed in 69% of the LV walls and most Duchenne boys had SPECT and ECG abnormalities in the posterior wall, which is the commonly involved site.[4] However, if 2 fibrous zones of equal size happen to be located oppositely, then a cancellation effect should make the electrocardiogram appear normal. Our patients occasionally exhibited multiple perfusion defects despite minimal ECG abnormalities, and both the anteroseptal and inferior walls showed no correlations between the 2 tests. Thus, as a logical extension of hypothesis (1), an electrocardiogram that appears normal despite SPECT hypoperfusion can be ascribed to a cancellation effect of the reciprocally reduced electromotive forces in the opposite walls. Consequently, the more profound the LV dystrophy, the more often ECG may underestimate LV fibrosis. In addition, our patients often showed hypoperfusion in the posteroapical wall despite the posterolateral electrocardiographic pattern. This was consistent with the report that an abnormal Q in leads I, aVL, V_5 and V_6 reflects apical rather than lateral scar in LV infarction.[28] Thus, the ECG pattern in muscular dystrophy may also mean posteroapical rather than posterolateral dystrophy. Hypothesis (2) is unlikely because ECG and SPECT showed no significant difference in incidence between groups with and without LV malrotations. However, an abnormal Q can be seen with a heart that is normal except for LV malrotation.[29] Because 49% of our patients had LV malrotations, probably due to kyphoscoliosis, ECG in muscular dystrophy may be complicated by both LV fibrosis and LV malrotation(s). A discussion of hypotheses (3) through (7) is beyond the scope of our paper. (We excluded such confounding electrocardiograms.) Nevertheless, based on our results, hypotheses (3) and (4)

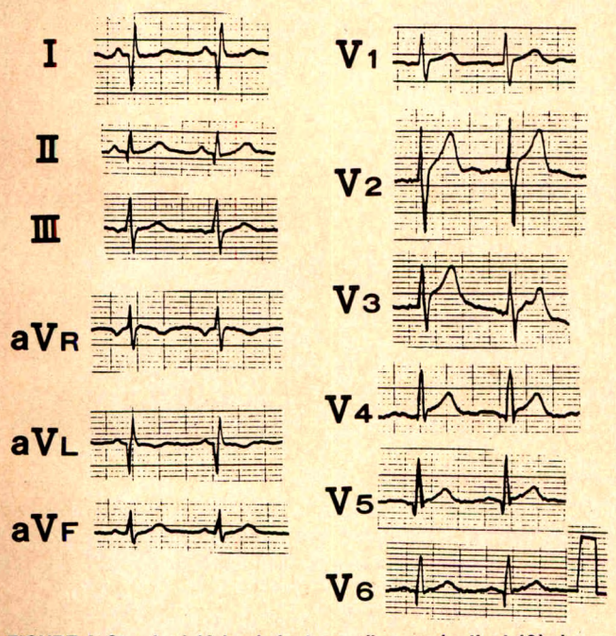

FIGURE 4. Standard 12-lead electrocardiogram (patient 13) shows low voltage in all leads. This is suggestive of both posterolateral wall injury—in terms of abnormally deep Q in leads I and aVL, increased R/S ratio (>1.0) in lead V_1 and diminished R in leads V_5 and V_6 (<1.0 mV)—and anterior wall injury—in terms of decreased R wave amplitude from V_2 to V_3. All calibrations are 1.0 mV.

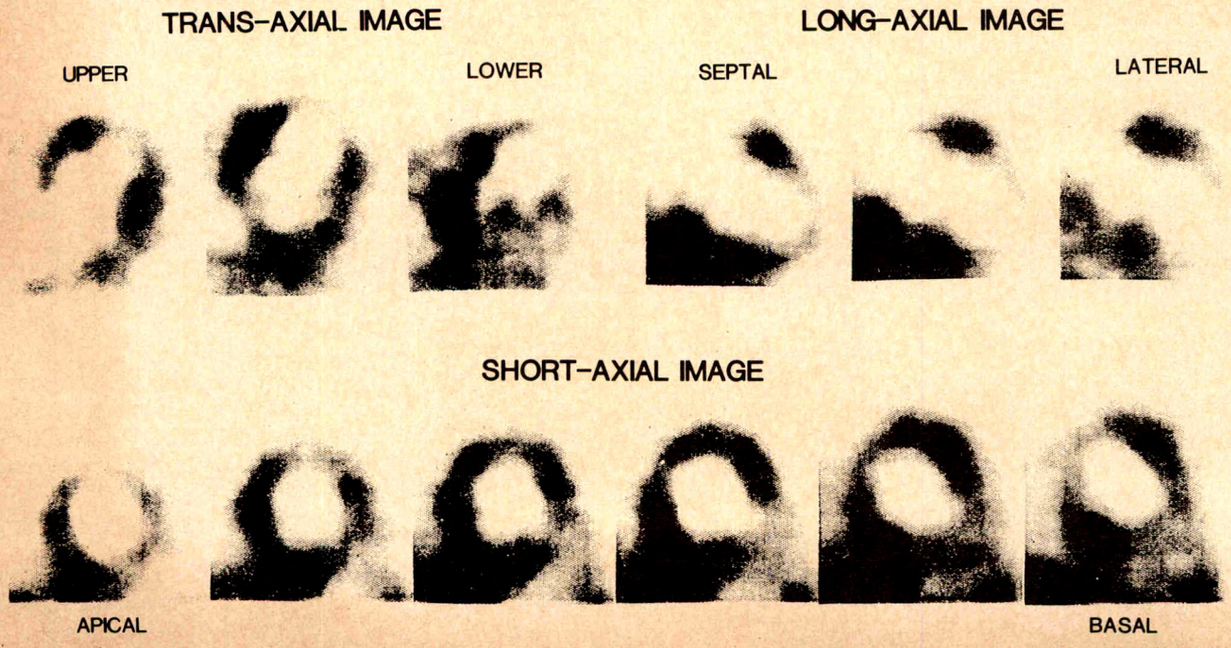

FIGURE 5. Thallium-201 computed tomograms (patient 13) showed diffuse loss of thallium uptake over all the LV walls, especially at the apical wall. The LV cavity was dilated and lung uptake of thallium was marked. Reproduced with permission from Kaku Igaku.[18]

seem unlikely because our SPECT images showed neither right ventricular nor septal hypertrophy and our electrocardiograms did not reveal an infarction pattern, i.e., a deep Q plus inverted T-wave.

In summary, the pathogenesis of an abnormal QRS in muscular dystrophy appears to involve: (1) as a primary effect, a reduced electromotive force in the dystrophic wall; (2) its cancellation effect in multiple lesions; (3) possible LV malrotation; (4) an age-factor[12,13] (in boys with Duchenne dystrophy). Thus ECG may have limited value in assessing the extent of LV dystrophy because it does not provide sufficient information on (2) and (3).

This study conventionally reported LV dystrophy as an "all or none" process in each wall, following the analytical methods of previous investigators.[1-7] Although we believe that SPECT had higher sensitivity for detection of the disease than ECG, further follow-up of our patients with both tests should be helpful in determining whether ECG underestimates or SPECT overestimates LV dystrophy.

The clinical stage showed correlation with neither SPECT nor ECG. This study showed individual variability for skeletal versus LV dystrophy and also revealed LV fibrosis in all 4 clinical types, as demonstrated by SPECT. Consequently, LV fibrosis may be a critical problem in this disease, irrespective of skeletal involvement and clinical subtype, and SPECT should be especially helpful in screening for this potentially fatal complication.

Acknowledgment: We thank Tetsutaro Abe, MS, Department of Radiology, Nagoya University School of Medicine, for technical assistance.

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Doppler Ultrasound Evaluation of Valvar Pulmonary Stenosis from Multiple Transducer Positions in Children Requiring Pulmonary Valvuloplasty

ELMAN G. FRANTZ, MD, and NORMAN H. SILVERMAN, MD

The modified Bernoulli equation has been used to determine the peak pressure difference across stenotic pulmonary valves. The direction of the poststenotic jet may be eccentric in relation to the axis of the pulmonary artery. Consequently, the maximal velocity obtained from the parasternal transducer position may inaccurately estimate peak pressure difference. Thus, Doppler-derived estimates of pressure difference from the parasternal, subcostal, apical, and suprasternal notch transducer positions were compared with peak-to-peak pulmonary artery to right ventricle catheter withdrawal pressure differences in 24 patients admitted for pulmonary valvuloplasty. Suprasternal, subcostal or apical transducer positions produced higher maximal velocities than the parasternal transducer position in 12 of 24 patients when the studies were performed before cardiac catheterization and in 8 of 12 patients when performed during cardiac catheterization. The Doppler-derived estimates using the highest maximal velocity predicted catheterization pressure difference accurately when the measurements were not performed simultaneously ($y = 1.05x - 3.3$, $r = 0.86$, standard error of the estimate $\pm$ 18.7 mm Hg) and the correlation was closer when the measurements were performed simultaneously ($y = 1.09x - 2.7$, $r = 0.97$, standard error of the estimate $\pm$ 9.4 mm Hg). The transducer position that yielded the highest maximal velocity in an individual patient was the same before and after valvuloplasty. In all groups, the correlation with pressure at cardiac catheterization was improved by using the highest maximal velocity rather than the parasternal maximal velocity.

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The application of the modified Bernoulli equation to estimate pressure differences across stenotic orifices requires axial alignment of the jet and the Doppler ultrasound beam.[1–3] This technique has become increasingly important for determining which children require valvuloplasty. Positioning the transducer in the left parasternal area and directing the ultrasound beam through the main axis of the pulmonary artery is the accepted approach to measure normal blood flow velocity in the main pulmonary artery[4–6] and to measure poststenotic maximal velocity in valvar pulmonic stenosis.[7,8] In valvar pulmonic stenosis, the direction of the poststenotic jet may deviate significantly from the ultrasound axis obtained from the parasternal transducer position, thereby adversely affecting the accuracy of the Doppler-derived estimate of pressure difference. The use of an alternative transducer position such as the subcostal, suprasternal notch or apical approach might result in a closer ultrasound beam alignment with the jet, allowing a more accurate estimate of pressure difference. With the advent of percutaneous balloon valvuloplasty for valvar pulmonic stenosis, appropriate timing of valvuloplasty can be aided by accurate Doppler-derived estimates of severity. The objective of this study was to determine whether the use of multiple transducer positions would improve the accuracy of estimation of pressure difference in children considered for balloon pulmonary valvuloplasty both before and after the procedure.

From the Department of Pediatrics, Division of Pediatric Cardiology, and the Cardiovascular Research Institute, University of California, San Francisco, California. This study was supported in part by training grant HL07544 from the National Institutes of Health, Bethesda, Maryland. Manuscript received October 5, 1987; revised manuscript received and accepted December 10, 1987.

Address for reprints: Norman H. Silverman, MD, M342A, University of California-San Francisco, Third and Parnassus Avenue, San Francisco, California 94143.

Methods

Patients: We identified 74 cases of isolated valvar pulmonic stenosis from January 1984 to October 1986. The patients' ages ranged from 1 day to 16 years. Forty-eight patients had undergone catheterization and continuous wave ultrasound studies. In the 24 patients who form the basis of this report, pulmonary artery velocity was recorded by Doppler ultrasound from more than 1 transducer position. Their ages ranged from 10 days to 13 years (mean 34 months ± 43 months standard deviation) and the median age at the time of study was 20 months.

Continuous wave Doppler echocardiographic studies were obtained on an IREX 3B system using a Pedoff 2-MHz continuous wave stand-alone transducer or on an ATL UltraMark 8 system, which uses a similar transducer. These small stand-alone transducers can be acutely angled in directions that larger transducers cannot achieve. The recordings were performed with the patient resting quietly in the left lateral decubitus position for the parasternal and apical transducer positions or supine for the subcostal transducer position. For the suprasternal notch transducer position the patient was supine with the neck extended and the head turned toward the right shoulder in order to obtain anterior alignment of the ultrasound beam. From each transducer position the transducer was angled to obtain the signal of highest velocity. The left parasternal area was evaluated with the transducer positioned in the second through fifth intercostal spaces and the highest velocity obtained was taken to represent the parasternal transducer position for analysis. Most studies were performed within the 18 hours before cardiac catheterization. The continuous wave Doppler signals were recorded on silver iodide paper at a speed of 50 mm/s, on one-half inch videotape for subsequent analysis or on both.

The continuous wave Doppler records were reviewed by one of us (EGF) without knowledge of catheterization results or prior echocardiographic interpretations. The Doppler signal was considered to be satisfactory when there was a well-defined outline of the envelope.[3] Maximal velocity was determined to the nearest 0.25 m/s. Doppler-estimated pressure differences were calculated by the simplified Bernoulli equation ($\Delta P = 4V^2$) and compared by linear regression analysis with measurements of peak-to-peak pressure difference obtained by pulmonary artery to right ventricle withdrawal during cardiac catheterization.

We studied 15 consecutive patients referred for pulmonary valvuloplasty prospectively. Continuous wave Doppler studies were performed during cardiac catheterization immediately after pulmonary artery to right ventricle catheter withdrawal before and after valvuloplasty. All Doppler recordings were obtained on an IREX 3B system without 2-dimensional guidance. The transducer position that produced the highest maximal velocity was assumed to approximate the axis of blood flow most closely. The Doppler signals were recorded and analyzed as already described without knowledge of cardiac catheterization findings. Adequate Doppler data from at least 2 transducer positions were obtained in 12 patients before valvuloplasty and in 10 patients after valvuloplasty. Doppler signals were not obtained from the apical transducer position in these patients. Peak-to-peak catheter pressure differences and Doppler-derived pressure differences from various transducer positions were compared by linear regression analysis.

To evaluate inter- and intraobserver variability, the maximal velocity of 50 of the Doppler recordings was interpreted by a second observer (NHS) and by the first observer (EGF) at a second reading without knowledge of prior interpretations. Interobserver variability was calculated as the difference between the 2 observers' readings divided by the average of their readings and expressed as a positive percentage. Intraobserver variability was calculated as the difference between the first observer's 2 readings divided by the average of the 2 readings and expressed as a positive percentage.[9]

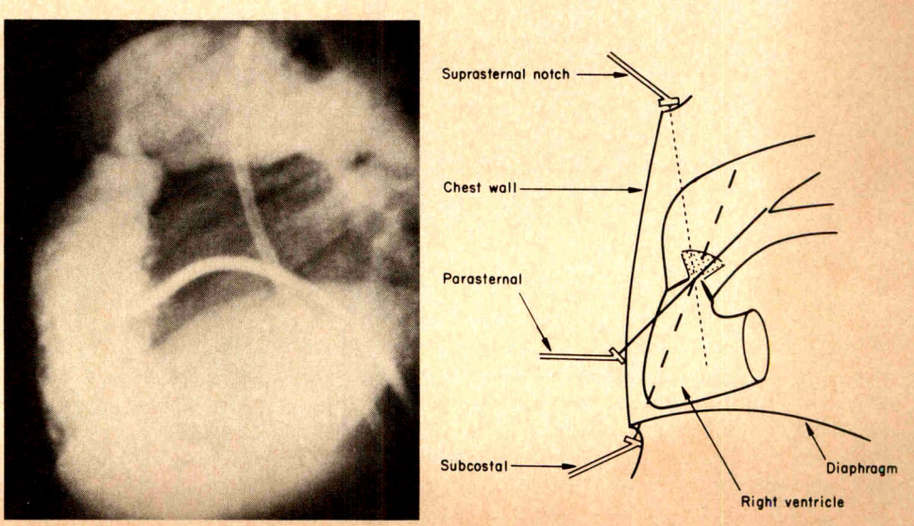

FIGURE 1. ***Left,*** **a lateral right ventricular angiogram showing an "eccentric" poststenotic jet in a patient with valvar pulmonic stenosis.** ***Right,*** **line drawing corresponding to angiogram showing the possible range of directions of a poststenotic jet (*shaded cone above pulmonary valve*) and the axis of ultrasound from multiple transducer positions.**

Results

Of the 48 patients who had nonsimultaneous catheterization and Doppler determinations of pressure difference, 24 had Doppler signals from parasternal and suprasternal, subcostal or apical transducer positions, 21 had parasternal signals alone and 3 had suprasternal signals alone. Of the 24 patients studied from multiple transducer positions, the maximal velocity from the parasternal transducer position was equal to or greater than the maximal velocity of the highest other transducer position in only 12 (50%). In the other 12 patients, a higher maximal velocity was obtained from the suprasternal, subcostal or apical transducer position. In a right ventricular angiogram obtained from 1 of the patients an anterosuperiorly directed poststenotic jet is demonstrated (Figure 1). Continuous-wave Doppler signals in this patient confirmed that suprasternal, subcostal and apical transducer positions produced higher maximal velocities that were more predictive of catheterization findings than the parasternal maximal velocity (Figure 2).

Linear regression analysis comparing nonsimultaneous Doppler-derived pressure differences using the parasternal transducer position versus catheterization pressure differences showed suboptimal strength of correlation ($r = 0.78$) with considerable variability (standard error of the estimate ± 20.6 mm Hg). More importantly, the least squares line of best fit ($y = 1.36x - 12.5$) deviated significantly from the line of identity reflecting underestimation of the more severe obstructions (Figure 3, top). When Doppler-derived pressure difference using the signal of highest maximal velocity (regardless of transducer position) was compared with catheterization pressure difference, the correlation was stronger ($r = 0.86$) with similar variability (standard error of the estimate ± 18.7 mm Hg) but the regression line ($y = 1.05x - 3.3$) very closely approximated the line of identity (Figure 3, bottom).

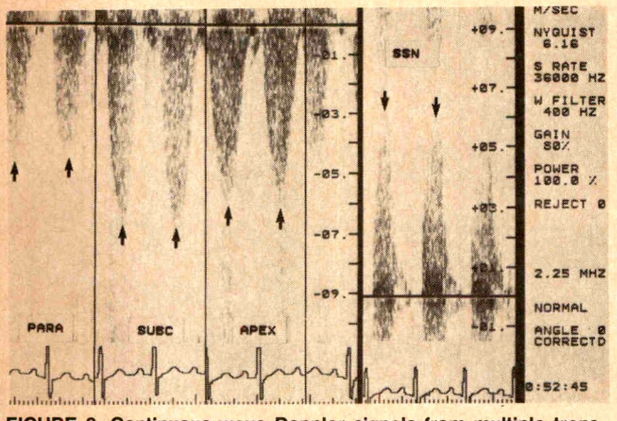

FIGURE 2. Continuous-wave Doppler signals from multiple transducer positions in the patient shown in Figure 1. Catheterization pressure difference was 154 mm Hg. The parasternal (PARA) maximal velocity is lower and less predictive than the subcostal (SUBC), apical (APEX) or suprasternal notch (SSN) maximal velocities (*arrowheads*). Note the inverted zero line and scale for the SSN velocities.

Of the 12 patients who underwent simultaneous catheterization and Doppler measurements before valvuloplasty, the parasternal maximal velocity was equal to or greater than the highest maximal velocity from a suprasternal or subcostal transducer position in only 4 (33%). A suprasternal or subcostal transducer position resulted in a higher maximal velocity than the parasternal transducer position in 8 patients (67%, Figure 4).

Despite the fact that the measurements in these 12 patients were made simultaneously, linear regression analysis resulted in a weak correlation ($r = 0.59$) with greater variability (standard error of the estimate ± 32.1 mm Hg) and poor approximation of the line of

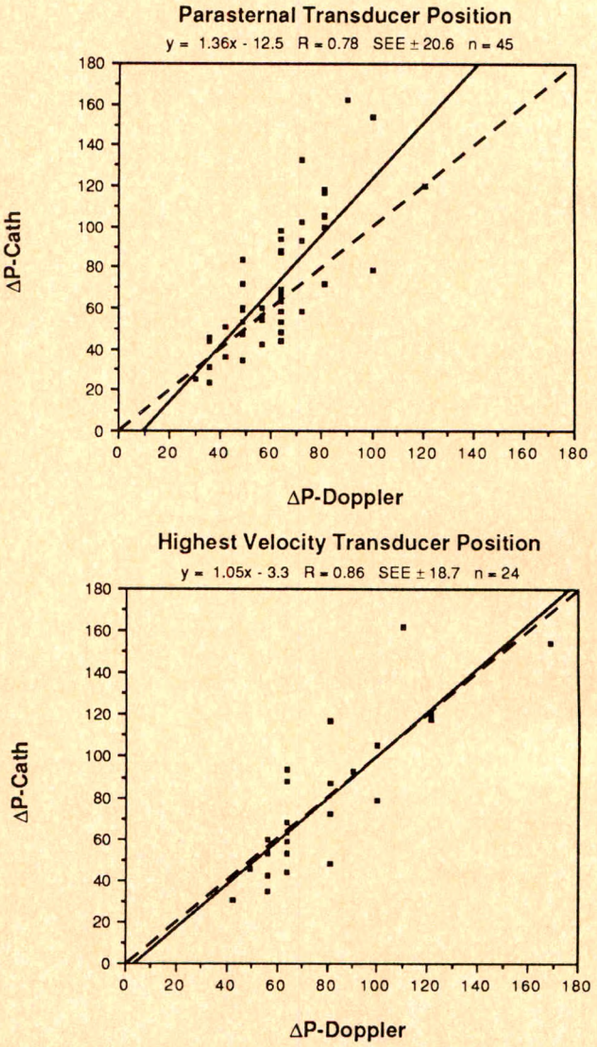

FIGURE 3. Linear regression plots comparing Doppler-derived pressure difference (ΔP Doppler) with catheterization pressure difference (ΔP Cath), both in mm Hg. At the *top*, ΔP Doppler was obtained using the nonsimultaneous parasternal maximal velocity in 45 patients. *Bottom*, ΔP Doppler was obtained using the highest maximal velocity regardless of transducer position in 24 patients. The *solid line* is the line of best fit. The *dashed line* is the line of identity.

identity (y = 1.36x + 5.1) when the parasternal signal was applied (Figure 5, top). However, the Doppler signals from the transducer position of highest maximal velocity correlated very strongly (r = 0.97) with catheterization measurements. The variability was reduced (standard error of the estimate ± 9.4 mm Hg) and the line of best fit (y = 1.09x − 2.7) closely approximated the line of identity (Figure 5, bottom).

After valvuloplasty, simultaneous Doppler and catheterization data were obtained in 10 patients. The parasternal signal (obtained in only 9 patients) was equal to or greater than the highest signal from the other position in only 4 patients (44%). The suprasternal or subcostal transducer position produced a higher maximal velocity in 5 patients (56%). An improved predictive accuracy using Doppler signals from the transducer position yielding the highest velocity is confirmed by linear regression analysis (Figure 6). The transducer position that yielded the highest velocity in an individual patient was the same before and after valvuloplasty.

Interobserver variability was 3.3 ± 4.3% (mean ± standard deviation) and intraobserver variability was 3.1 ± 3.9%. Linear regression analysis provides an interobserver correlation of y = 1.01x + 0.03, r = 0.97, standard error of the estimate ± 0.23 m/s and an intraobserver correlation of y = 0.95x + 0.09, r = 0.98, standard error of the estimate ± 0.17 m/s. In no patient was more than a 1/4 m/s difference found between the 2 observers' readings in any view.

Discussion

The parasternal transducer position has been the standard portal for the evaluation of valvar pulmonic stenosis by Doppler echocardiography. Oliveira Lima et al[7] reported a very high accuracy of prediction of nonsimultaneous catheterization findings by Doppler-estimated pressure difference in 16 patients using only the parasternal transducer position. Kosturakis et al,[8] also using only the parasternal approach, achieved acceptable predictive accuracy in 11 patients although some severe obstructions were underestimated. We were unable to achieve this degree of accuracy using parasternal measurements alone. In contrast, we identified patients in whom the parasternal approach alone had seriously underestimated true pressure difference at subsequent cardiac catheterization and, thus, led to this investigation.

Multiple Doppler transducer positions have been used in adults for the evaluation of aortic stenosis[10]

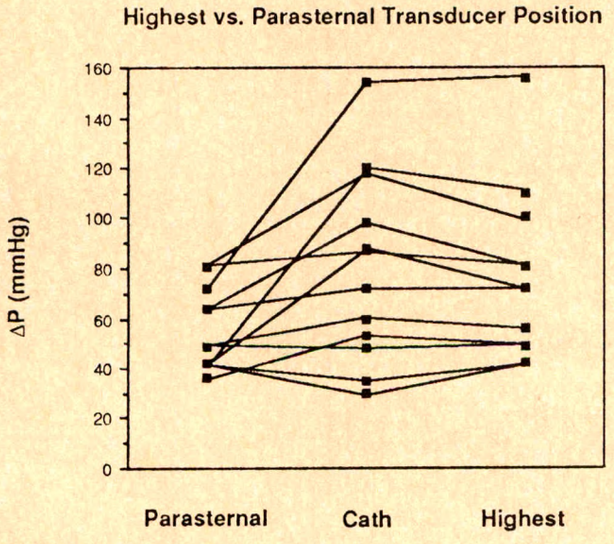

FIGURE 4. Patient-by-patient comparison of pressure difference (ΔP) predicted by the parasternal maximal velocity (*left*), the highest maximal velocity regardless of transducer position (*right*) or measured at catheterization (Cath, *middle*). Individual patient values are connected by lines.

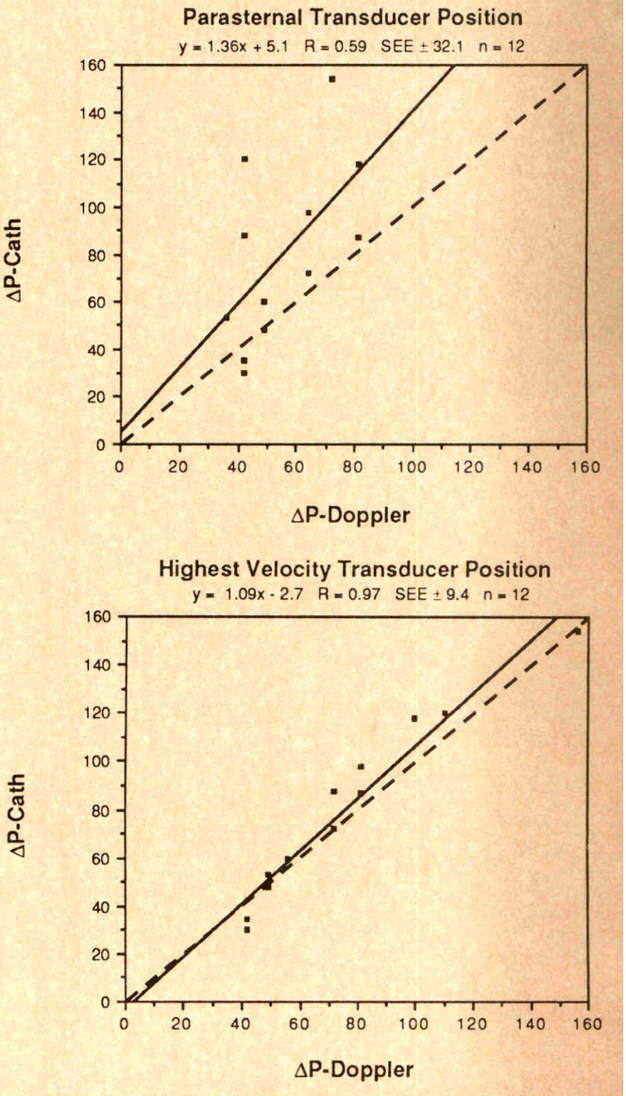

FIGURE 5. Linear regression plots comparing Doppler-derived pressure difference (ΔP Doppler) with catheterization pressure difference (ΔP Cath), both in mm Hg, before valvuloplasty. *Top*, ΔP Doppler was obtained using the simultaneous parasternal maximal velocity. *Bottom*, ΔP Doppler was obtained using the highest maximal velocity regardless of transducer position. The *solid line* is the line of best fit. The *dashed line* is the line of identity.

and nonstenotic pulmonary[11] and aortic[12] blood flow. Williams et al[10] reported improved assessment of aortic stenosis using 3 transducer positions, although the highest of 3 signals was only marginally more accurate than the apical signal alone. Stevenson and Kawabori[13] used both parasternal and subcostal approaches in applying modified pulsed Doppler systems to high velocity poststenotic flow in children with pulmonic stenosis but did not comment on the relative accuracy of the 2 transducer positions. Johnson et al[14] measured maximal velocities from the parasternal and subcostal approaches in 12 children with valvar pulmonic stenosis, but the subcostal signal substantially improved the prediction of catheterization pressure difference in only 1 patient. Murphy et al[15] also have supported the use of subcostal imaging but have suggested that the suprasternal position does not provide adequate alignment of the ultrasound beam. Based on these studies, the value of multiple transducer positions in valvar pulmonic stenosis had not previously been conclusively demonstrated.

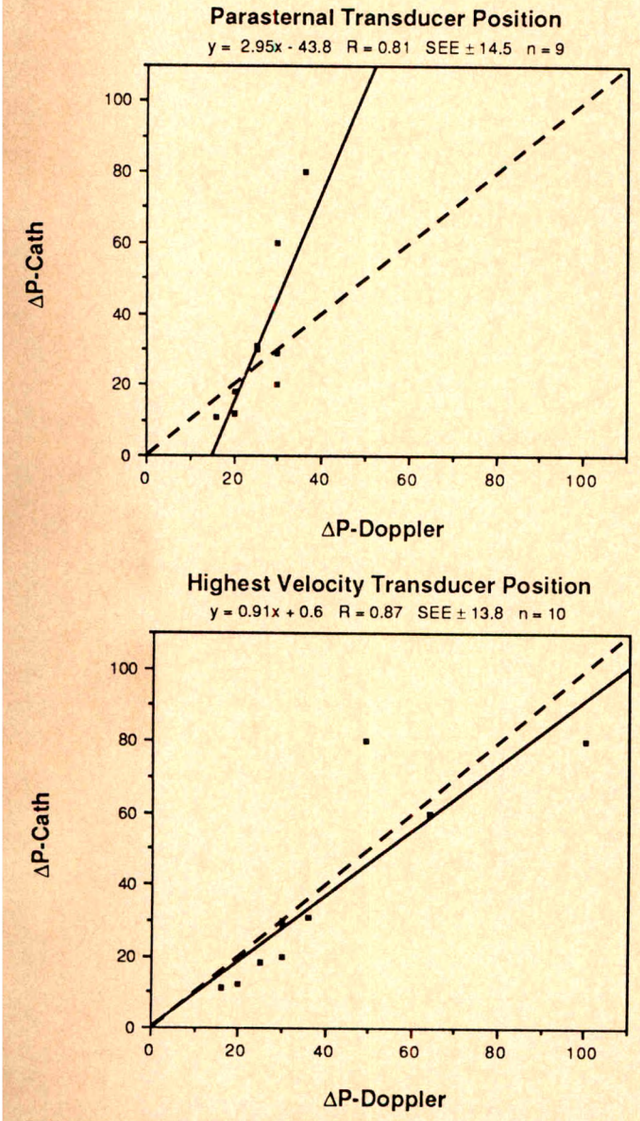

FIGURE 6. Linear regression plots comparing Doppler-derived pressure difference (ΔP Doppler) with catheterization pressure difference (ΔP Cath), both in mm Hg, after valvuloplasty. At *top*, ΔP Doppler was obtained using the simultaneous parasternal maximal velocity. *Bottom*, ΔP Doppler was obtained using the highest maximal velocity regardless of transducer position. The *solid line* is the line of best fit. The *dashed line* is the line of identity.

Our results, however, demonstrate superior prediction of catheterization pressure differences by applying the Bernoulli equation to the highest velocity signal obtained from multiple transducer positions. The direction of the poststenotic jet in valvar pulmonic stenosis is unknown and varies from patient to patient; thus, the transducer position that will produce the closest alignment with this jet and the highest velocity cannot be anticipated. In our 10 patients in whom echocardiographic studies were performed before and after valvuloplasty, the transducer position producing the highest velocity in an individual was not altered. However, because our sample size is small, we cannot generalize to the population at large. The direction of the poststenotic jet might be altered by valvuloplasty in some patients. For these reasons, multiple transducer positions should be used in each patient before and after valvuloplasty.

Several other findings of our study are notable. The highest Doppler velocities recorded at cardiac catheterization (Figure 5, bottom) more accurately predicted catheterization pressure difference than the highest velocities not recorded simultaneously (Figure 3, bottom). This may be due to the level of sedation and transvalvar flow rate, which were nearly identical in the former group and highly variable in the latter. A poor correlation was found using the parasternal velocities obtained at cardiac catheterization. (Figure 5, top), which might be related to technical limitations of performing Doppler echocardiography in the catheterization laboratory where optimal patient position and time constraints may have had an adverse impact on the Doppler study.

In 7 of 24 patients (29%) with nonsimultaneous measurements (Figure 3), Doppler-derived pressure difference overestimated catheterization findings by at least 10 mm Hg. Level of arousal and, thus, cardiac output are likely to be greater in unsedated outpatients than in sedated patients undergoing catheterization. Doppler-derived measurements are known to overestimate simultaneous peak-to-peak catheterization measurements and to correlate more closely with peak instantaneous pressure differences.[16,17] Nonetheless, we and others have found excellent predictive accuracy with peak-to-peak measurements without overestimation.[7,8,13,14] Accurate Doppler-derived estimates of severity especially in the range of values where treatment may be contemplated are valuable because they influence timing of balloon valvuloplasty and aid in the accurate follow-up thereafter.

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Anomalous Origin of a Pulmonary Artery from the Ascending Aorta: Associated Anomalies and Pathogenesis

LYNN M. KUTSCHE, MD, and L.H.S. VAN MIEROP, MD

The pathologic anatomic features and associated cardiovascular anomalies of 9 patients with anomalous origin of 1 pulmonary artery (PA) from the ascending aorta seen at the University of Florida and 99 previously reported cases were analyzed. Anomalous origin of the right PA was much more common than anomalous origin of the left PA. The anomalous right PA usually arose from the posterior aspect of the ascending aorta close to the aortic valve. Less commonly, it originated from the lateral ascending aorta just proximal to the innominate artery. Patent ductus arteriosus and aorticopulmonary septal defect were commonly associated with anomalous origin of the right PA; other cardiovascular anomalies were rare. In contrast, tetralogy of Fallot and aortic arch anomalies, e.g., right aortic arch and anomalous origin of the subclavian artery, were common in anomalous origin of the left PA. An association with DiGeorge syndrome, frequently noted with persistent truncus arteriosus, was not seen with anomalous origin of a PA from the ascending aorta. The observations indicate that anomalous origin of the right PA and anomalous origin of the left PA are pathogenetically unrelated to each other and both are unrelated to persistent truncus arteriosus. Moreover, anomalous origin of the right PA arising close to the innominate artery is thought to be pathogenetically distinct from the type that arises close to the aortic valve. These pathogenetic relations should be considered in epidemiologic studies of congenital heart disease.

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Anomalous origin of either the right or the left pulmonary artery (PA) from the ascending aorta is rare. The anomaly has been considered a partial form of persistent truncus arteriosus by some or to be due to abnormal truncal septation.[1-6] Some believe anomalous right PA to be the result of lack of leftward migration of the right sixth aortic arch,[7-10] while others consider it to represent a persistence of either the right fifth or distal right sixth arch with early involution of the proximal arch.[11-15]

In a recent review of cardiac anomalies associated with DiGeorge syndrome, interrupted arch type B and persistent truncus arteriosus were found in 48 (30%) and 37 (23%) patients, respectively, but not a single case of anomalous origin of a PA from the ascending aorta or aorticopulmonary septal defect was seen.[16] This seemed odd since both anomalies involve a region between the aortic and pulmonary roots and the aortic arch system. Moreover, both have been considered to be partial forms of persistent truncus arteriosus and therefore pathogenetically related. This stimulated us to review our own cases of anomalous origin of the PA from the ascending aorta as well as those reported previously by others.

Methods

Seven cases of anomalous origin of a PA from the ascending aorta were found among 7,329 patients with

From the Department of Pediatrics (Divisions of Research and Cardiology) and Pathology, University of Florida College of Medicine, Gainesville, Florida. Dr. Kutsche is the recipient of Clinical Investigator Award 5K08 HL00885 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received October 19, 1987; revised manuscript received and accepted December 10, 1987.

Address for reprints: Lynn M, Kutsche, MD, Department of Pediatrics, Division of Research, Box J-296, JHMHC, J. Hillis Miller Health Center, University of Florida, Gainesville, Florida 32610.

congenital heart disease seen at the University of Florida. Of these, 5 had anomalous origin of the right PA; in 2 cases the anomalous artery was on the left. Six patients had cardiac catheterization and surgery, the seventh case was examined at autopsy. Two cases, one each of anomalous right and left PA studied by one of us (LHSVM) at the Montreal Children's Hospital, are included in this report. A review of previous publications yielded 99 cases, 83 with anomalous right PA and 16 with anomalous left PA.[1,3-8,10,12-15,17-59] Reported cases were included only if individual case descriptions were given, so that associated anomalies could be analyzed.

Results

Data concerning our 9 cases are listed in Table I. Those concerning the 99 previously reported cases are summarized in Table II. We will now consider all 108 cases together.

Anomalous origin of the right pulmonary artery: In 76 of the 89 cases (85%) the anomalous PA arose proximally from the posterior or left posterior aspect of the ascending aorta close to the aortic valve (Figure 1D). In 13 case (15%) it originated from the ascending aorta just proximal to the innominate artery or from the base of the artery itself (Figure 1B). In 7 of the 13, the anomalous right PA was narrowed, usually some distance from its origin. All patients had a left aortic arch and over two-thirds had a patent ductus arteriosus. Aorticopulmonary septal defect was a common associated anomaly (15%) in those in whom the anomalous PA arose proximally but was seen only in one with distal origin of the PA. Tetralogy of Fallot was present in only 3 cases (3%); in 1 of these the right PA arose close to the innominate artery. Interruption of the aortic arch type A or coarctation of the aorta was associated in 11 cases of proximal right PA origin; 8 of these also had an aorticopulmonary septal defect.

Anomalous origin of the left pulmonary artery: In these 19 cases the artery usually arose from the left lateral aspect of the ascending aorta close to the aortic valve and curved upwards and over the left main bronchus to enter the left lung (Figure 1C). Tetralogy of Fallot was associated in 74% of the patients, a right aortic arch (with or without tetralogy of Fallot) was present in 63%. All 19 patients had either tetralogy of Fallot, a right aortic arch, or both. Nine (47%) had an anomalous origin of the subclavian artery. None had an associated aorticopulmonary septal defect, interruption of the aortic arch type A or coarctation of the aorta. The ductus arteriosus was patent in 16%. It was on the right, associated with a right aortic arch, in all. In another 20% there was no trace of even a ligamentum arteriosum.

Thus, aorticopulmonary septal defect is common in anomalous origin of the right PA from the ascending aorta, and tetralogy of Fallot and aortic arch anomalies are the rule in anomalous origin of the left PA. We believe that interruption of the aortic arch type A and coarctation, associated in most cases with aorticopulmonary septal defect, are secondary, hemodynamically induced anomalies.

TABLE I Major Findings in Nine Cases of Anomalous Origin of One Pulmonary Artery from the Ascending Aorta

Case	Age*, Sex	Major CV Anomaly	Other Cardiovascular Anomalies
1	8 days, F	AOLPA	RAA, ALSA, PDA, ASD
2	5 yrs, M	AOLPA	TF, RAA, ALSA
3	5 yrs, F	AOLPA	TF, ARSA, PLSVC
4	3 wks, F	AORPA	PDA
5	5 days, M	AORPA	None
6	3 mos, F	AORPA	PDA
7	3 mos, M	AORPA	APSD, IAA-A, PDA
8	2 mos, M	AORPA	PDA
9	1 yr, F	AORPA	PDA

* At surgery or autopsy.

AL(R)SA = anomalous left (right) subclavian artery; AOL(R)PA = anomalous left (right) pulmonary artery; APSD = aorticopulmonary septal defect; ASD = atrial septal defect; CV = cardiovascular; IAA-A = interrupted aortic arch type A; PDA = patent ductus arteriosus; PLSVC = persistent left superior vena cava; RAA = right aortic arch; TF = tetralogy of Fallot.

TABLE II Anomalous Origin of One Pulmonary Artery from the Ascending Aorta in 99 Reported Cases

	Proximal—AORPA—Distal				AOLPA	
	No.	(%)	No.	(%)	No.	(%)
Total	70	(100)	13	(100)	16	(100)
Sex						
M	43	(61)	7	(54)	8	(50)
F	22	(32)	6	(46)	7	(44)
Unknown	5	(7)	—	(—)	1	(6)
Associated CV anomaly						
TF	2	(3)	1	(8)	12	(75)
APSD	10	(14)	1	(8)	0	(0)
RAA	0	(0)	0	(0)	10	(63)
ASA	3	(4)	0	(0)	6	(38)
PDA	45	(64)	9	(69)	2	(13)
COA	3	(4)	1	(7)	0	(0)
IAA-A	6	(9)	0	(0)	0	(0)
IAA-B	0	(0)	1	(8)	0	(0)

COA = coarctation of the aorta. IAA-B = interrupted arch type B; other abbreviations as in Table I.

Embryology

The original arrangement in early vertebrate embryos of (usually) 6 pairs of branchial arch arteries (in mammalian embryology customarily referred to as the aortic arches), which connect the ventral aorta to the initially paired dorsal aorta, is retained into adulthood only in gill breathing fishes. With the advent of pulmonary respiration and loss of gills however, the aortic arch system undergoes profound modifications. In young embryos of airbreathing vertebrates the first 4 aortic arches and the primordia of the pulmonary arteries arise from a manifold-like structure, the (trunco) aortic sac (Figure 2). An invagination of the dorsal wall of the aortic sac between the fourth and the fused sixth arches (actually the pulmonary arteries[60,61] see below),

the aorticopulmonary septum, joins the distal face of the truncoconal septum, which meanwhile has divided the truncal part of the early embryonic heart into aortic and pulmonary roots.[62] The first 2 aortic arches involute and nearly disappear. In mammals the third arches become the common carotid and proximal in-

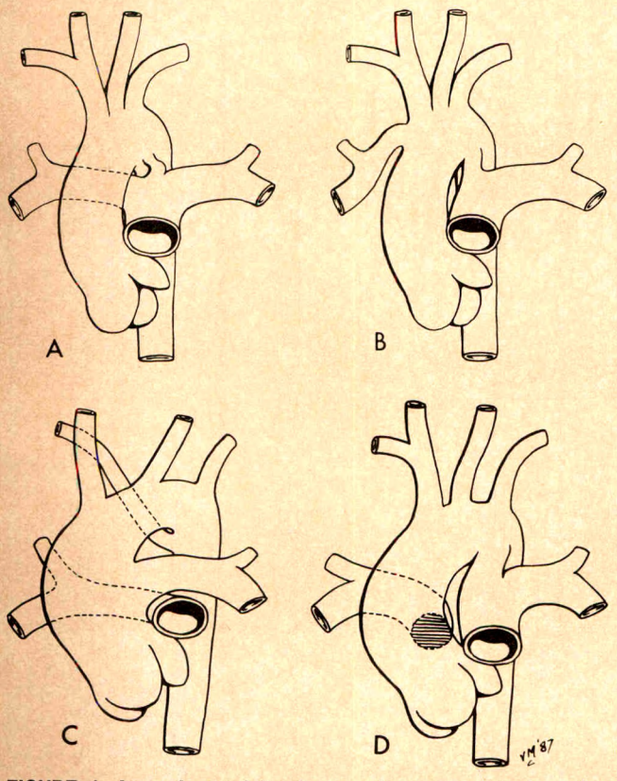


FIGURE 1. Anomalous origin of one pulmonary artery from the ascending aorta. *A*, normal; *B*, distal origin of right pulmonary artery; *C*, anomalous origin of left pulmonary artery (case 3); *D*, proximal origin of the right pulmonary artery (case 6).

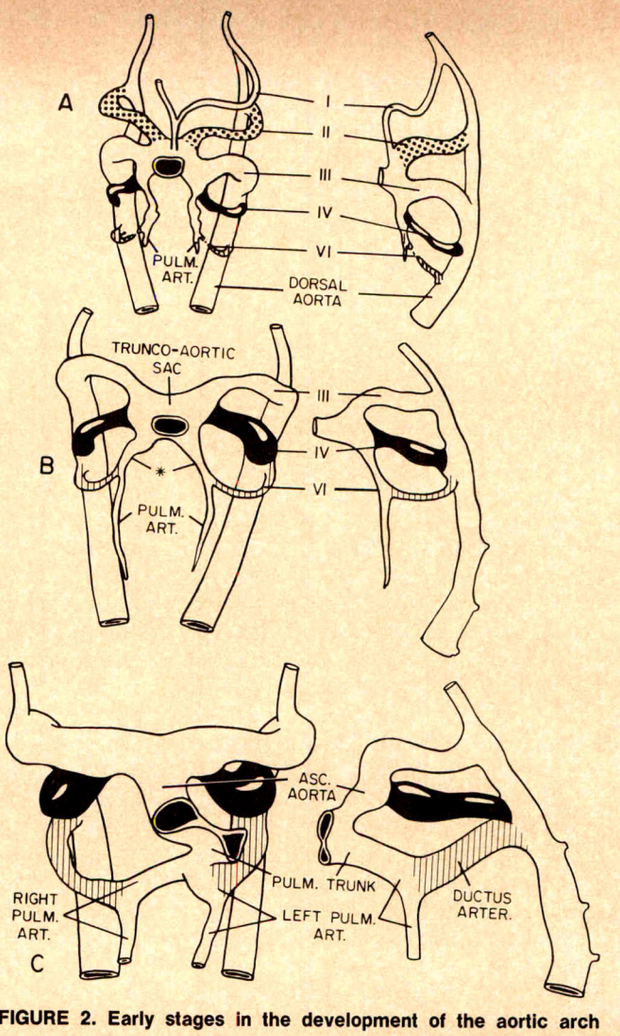
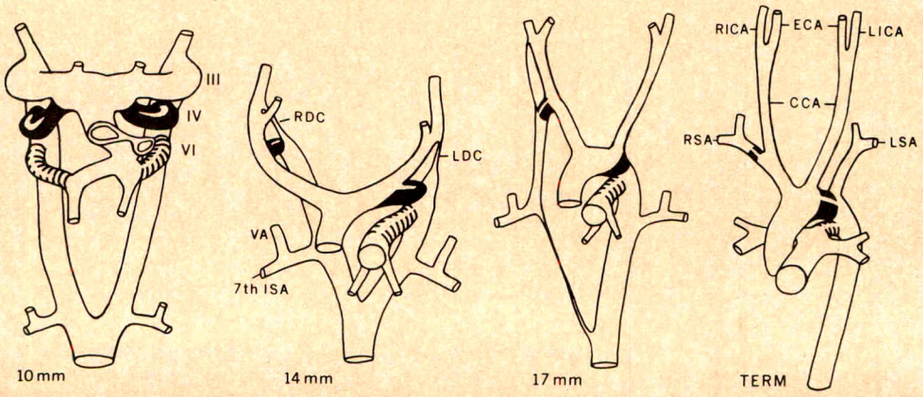


FIGURE 2. Early stages in the development of the aortic arch system. *Asterisk* indicates part of pulmonary artery usually and erroneously considered proximal part of sixth arch. ART = artery; ARTER = arteriosus; ASC = ascending; PULM = pulmonary (redrawn after Congdon[63]); A = 4 mm; B = 5 mm; C = 11 mm embryo.

FIGURE 3. Late stages in the development of the aortic arch system, to show the development of the right subclavian artery and the relationships between the distal (dorsal) parts of the fourth and sixth arches and the ascending aorta. III, IV and VI = third, fourth and sixth aortic arches; 7th ISA = seventh intersegmental artery; CCA = common carotid artery; ECA = external carotid artery; L (R) DC = left (right) ductus caroticus; L (R) ICA = left (right) internal carotid artery; L (R) SA = left (right) subclavian artery; RDA = right dorsal aorta; VA = vertebral artery. Reproduced with permission from Kutsche et al,[70] Am J Cardiol.



ternal carotid arteries. The left fourth arch becomes part of the normal aortic arch and its right counterpart forms part of the proximal right subclavian artery (Figure 3). The right and left sixth branchial arches first appear as ventral and much larger dorsal buds arising from the already existing pulmonary arteries[60,61] (derived from the ventral pharyngeal plexus, Figure 2) and dorsal aorta, respectively. As Bremer[60] points out, the pulmonary arteries, from a developmental point of view, strictly speaking are not branches of the sixth arches (a misconception perpetuated by the well-known Rathke's diagram[63] and its various modifications). Rather, the sixth arches connect the primitive pulmonary arteries to the dorsal aortae. After completion of the sixth arch in 5 to 6 mm embryos the proximal part of the early embryonic PA is usually but erroneously considered to be the ventral part of the sixth arch with the PA then arising from this arch. The ductus arteriosus therefore is *all* of the sixth arch, not just its dorsal part as is usually stated. The right PA migrates to the left and proximally fuses with the left to create the distal most part of the pulmonary trunk.[60,61,64]

The right sixth arch exists only briefly, the left sixth arch is retained until after birth as the ductus arteriosus. The fifth aortic arches, already smaller than the third, fourth, and sixth in amphibians, is reduced further in birds and mammals. In higher mammals including man, if present at all, it is usually rudimentary and makes its appearance after the sixth arch. In human embryos of 7 to 9 mm CR length it is present transiently.

Although the fifth aortic arch is rudimentary in higher mammals, man is among the few species in which it may be quite well developed. In reconstructed models of 7 embryos in which the pulmonary arch was almost or just completed, Congdon[61] found 3 instances of well-developed fifth arch vessels arising from the aortic sac or proximal fourth arch and joining the distal end of the pulmonary (sixth) arch. Although Congdon did not refer to these vessels as fifth aortic arches, his rather lengthy discussion and illustrations leave little doubt as to their true nature. Tandler[65] was the first to describe the embryonic fifth arch in 2 human embryos. Coulter[66] comments that "the typical mammalian 5th aortic arch appears to be a vessel which arises from the aortic bulb and empties into the pulmonic arch near its junction with the dorsal aorta. The development is most complete in man and the mole, in which an unbroken arch is the rule." He finds the fifth arch also to be present, be it in much more rudimentary form, in the cat, pig and rabbit. That a fifth arch can and does occasionally develop in man finds further support in the description of several cases of this arch persisting postnatally.[67,68]

Discussion

We concur with the interpretation that in cases of a pulmonary artery arising from the innominate artery as a trifurcation with the internal carotid and subclavian arteries or from the undersurface of the mid-aortic

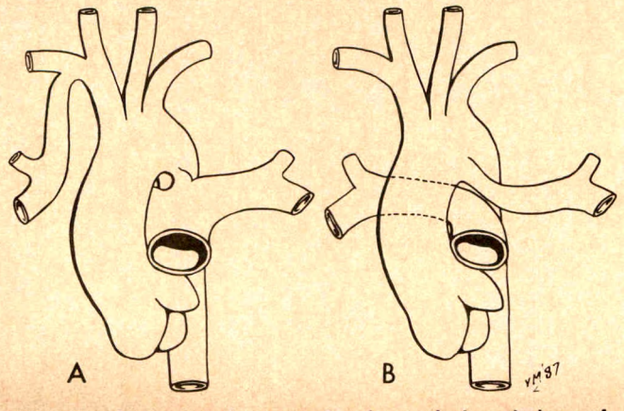


FIGURE 4. Origin of a pulmonary artery from a ductus arteriosus. *A*, from right subclavian artery; *B*, from aortic arch.

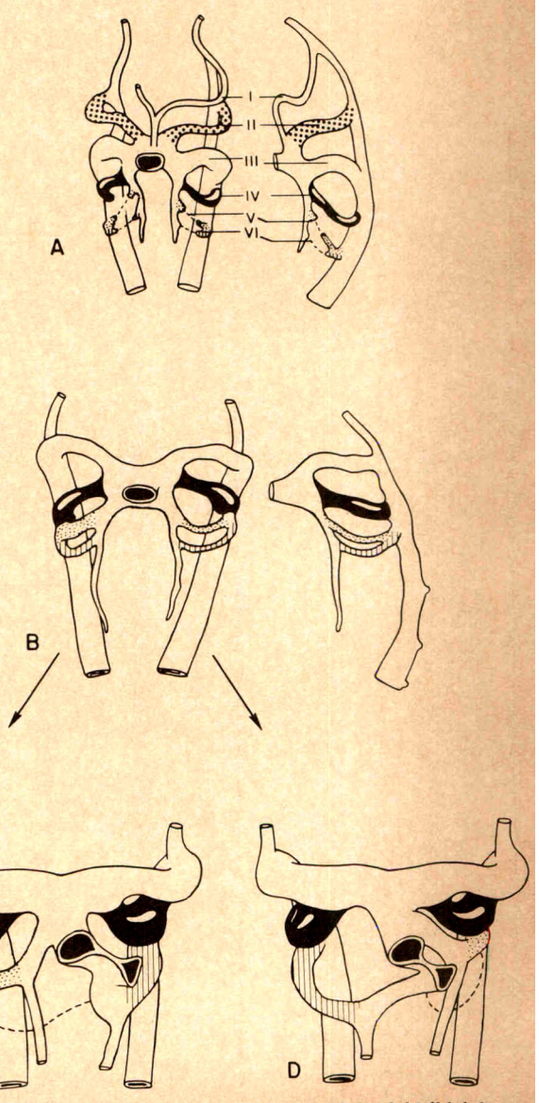


FIGURE 5. Pathogenetic mechanism of anomalous right (high type, *A*, *B*, *C*) and left pulmonary artery (*A*, *B*, *D*) if fifth arch is the dominant or only arch.

arch (Figure 4A and B), the proximal part of the anomalous PA in fact represents the ductus arteriosus, the proximal part of the embryonic pulmonary artery having retrogressed and disappeared early in development. The often reduced diameter of the proximal PA and the presence of ductal type tissue supports this view.

Anomalous origin of the right pulmonary artery: We agree with Schneiderman[10] and others[7-9] that in the proximal form of the anomaly the origin of the right PA from the left posterior aspect of the ascending aorta leave little doubt that the anomaly is due to incomplete (or delayed?) leftward migration of the right PA. The aorticopulmonary septum invaginates to its left rather than to its right as it does normally and leaves the right PA "stranded." The common association of aorticopulmonary septal defect is of interest in this regard since that anomaly may in some cases be due to malalignment of the aorticopulmonary and truncal septa.[69] The frequent association of aorticopulmonary septal defect with interruption of the aortic arch type A or coarctation is not coincidental and supports the proposal that the combination of anomalous origin of the right PA, distal aorticopulmonary septal defect and interruption of the aortic arch type A be considered a syndrome.[7] It is possible, however, that in some cases with the distal form of aorticopulmonary septal defect, in which the aorticopulmonary septum does not develop at all, the apparent anomalous origin of the right PA from the aorta is an illusion.

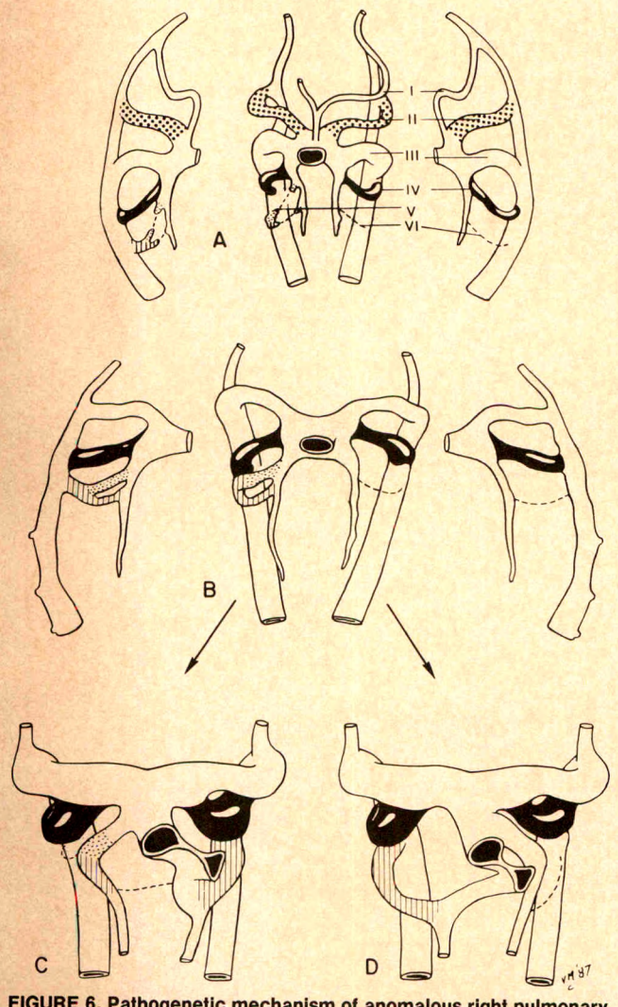


FIGURE 6. Pathogenetic mechanism of anomalous right pulmonary artery (distal origin *A*, *B*, *C*) if both fifth and sixth arches develop, and anomalous left pulmonary artery if neither fifth nor sixth arch develops. (See text.)

It is unlikely that the proximal right PA in cases in which it originates from the ascending aorta near the base of the innominate artery represents the ductus arteriosus, since the right fourth aortic arch forms part of the origin of the right subclavian artery (Figure 3). Three other, more plausible explanations for the anomaly are: (1) a right fifth arch developed and the sixth either did not or, if it did, it involuted early[11] (Figure 5A,B,C); (2) neither the fifth nor the sixth arch developed and the early embryonic PA retained its original position near the origins of the third and fourth arches, thus eventually appearing to have migrated up the ascending aorta rather than moving away from the third and fourth arches and occupying a position closer to the heart as it does normally (Figure 6A,B,D for anomalous origin of the left PA); or (3) a fifth arch developed, and the proximal PA as well as the distal (dorsal) part of the sixth arch disappeared, as it normally does (Figure 6A,B,C). This pathogenetic mechanism, proposed by Odell and Smith,[14] could explain the observation that a narrowing, as is present in about half the cases, usually does not involve the first part of the anomalous artery but is located further distal. The narrow area in some cases has been shown to contain ductal-type tissue. This may be the most likely pathogenetic mechanism, because associated cardiovascular anomalies involving the aortic arch system are not particularly common.

Anomalous origin of the left pulmonary artery: We do not find the theory by Cucci et al,[2] which for its pathogenetic explanation invokes a major abnormality of truncoconal septation, to be plausible because it does not explain the frequently associated aortic arch anomalies and any such deviation of aorticopulmonary septation might be expected to create a spectrum of abnormalities, not an either (normal)/or (anomalous origin) condition. We believe it more plausible that anomalous origin of the left PA from the proximal ascending aorta pathogenetically is an aortic arch anomaly, particularly since all known cases have been associated with tetralogy of Fallot, aortic arch anomalies, or both. A pathogenetic mechanism similar to that described previously for distal origin of the right PA from the ascending aorta, i.e., persistence of the left fifth arch with absence of the sixth or simply absence of the sixth arch, could also be invoked. Failure of development of the left sixth arch we believe to be the most likely cause for the anomaly. Finally, from an epidemiologic point of view it is important to bear in mind that the 3 forms of anomalous origin of a PA from

the ascending aorta are unrelated pathogenetically and none should be considered partial types of persistent truncus arteriosus.

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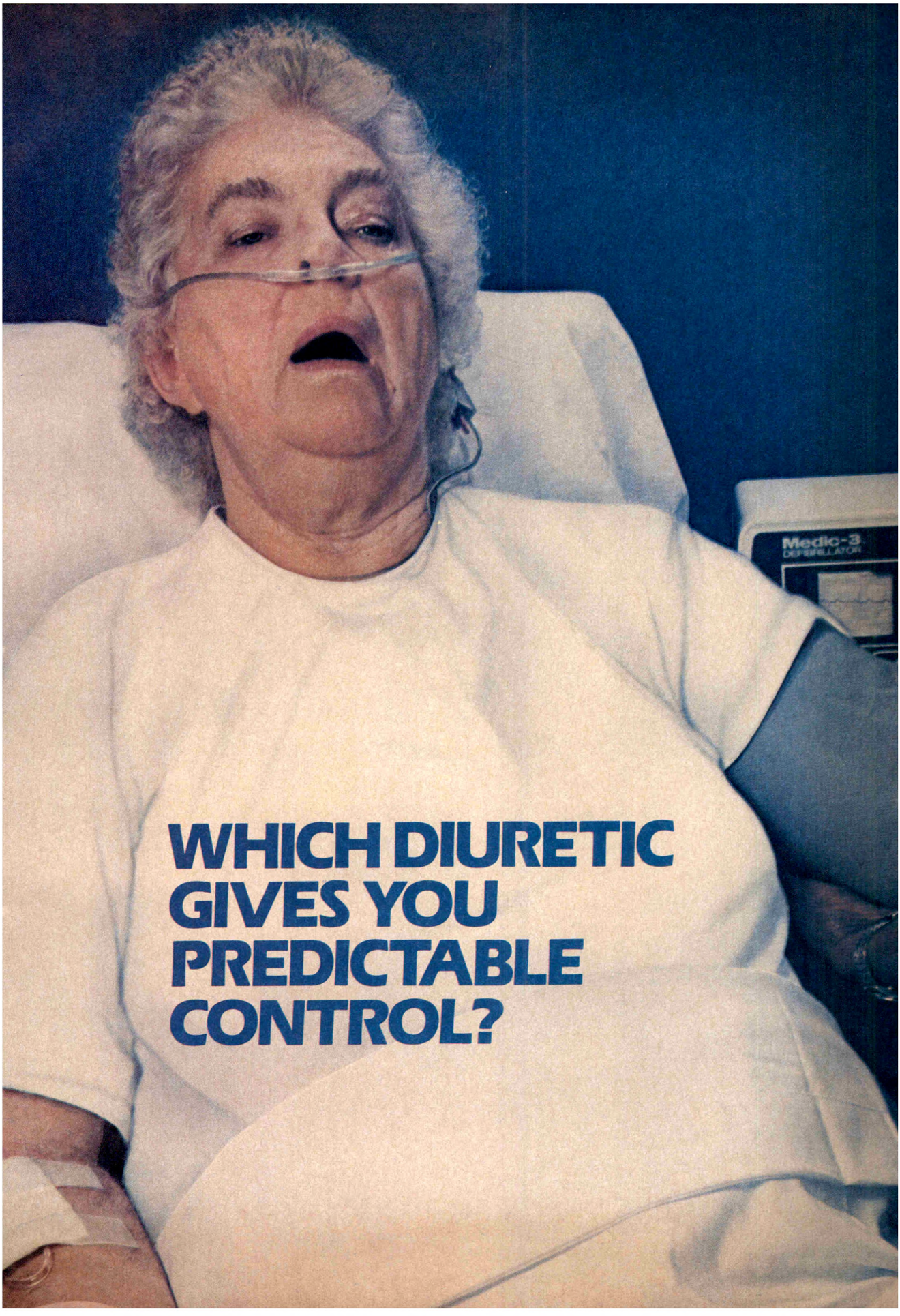
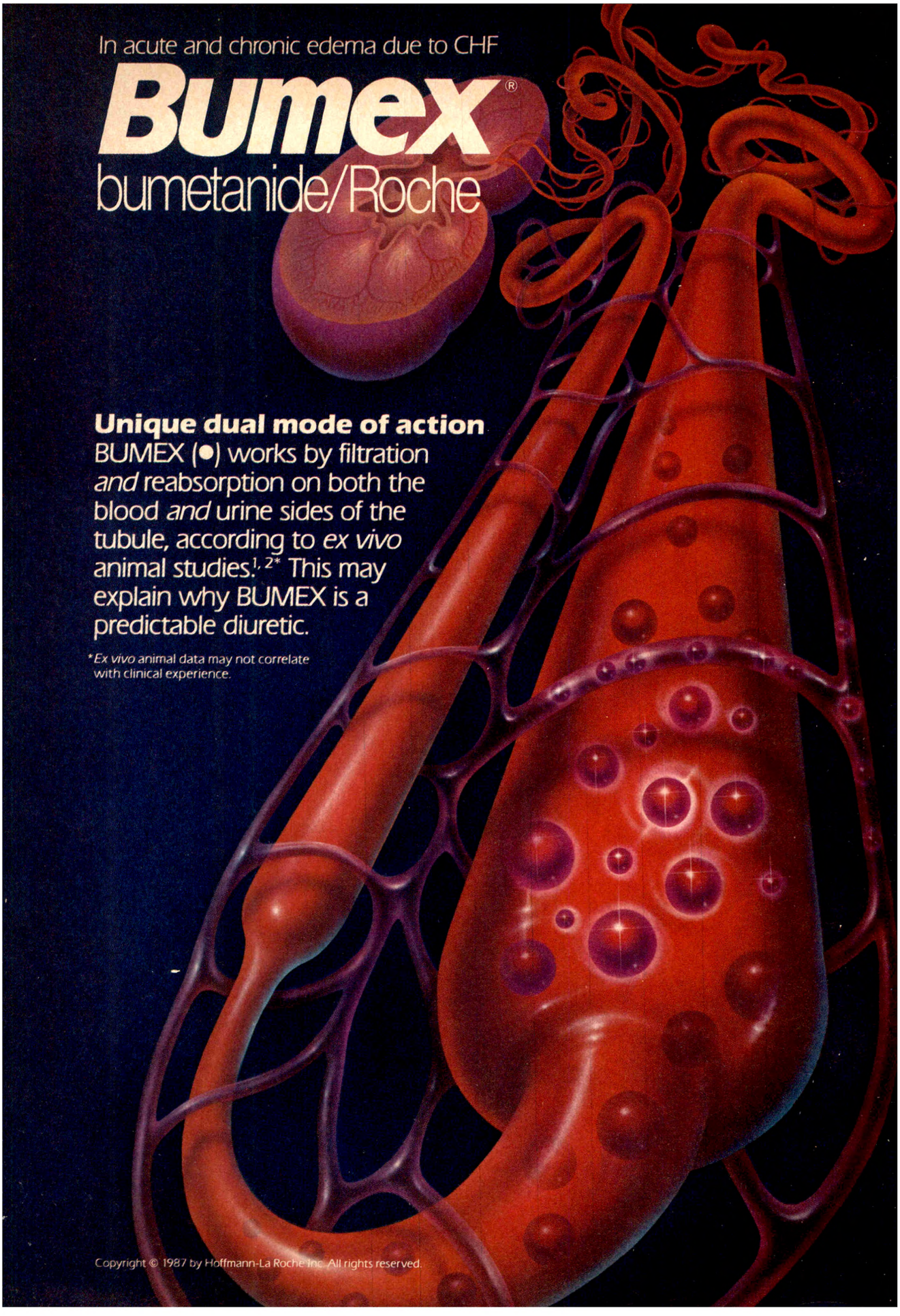


WHICH DIURETIC GIVES YOU PREDICTABLE CONTROL?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Less potassium loss for a given amount of sodium excretion than with furosemide.[3-5] As with all loop diuretics, excessive doses of BUMEX can lead to profound diuresis with water and electrolyte depletion, including hypokalemia, so serum electrolytes should be monitored.

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Please see adjacent page for references and summary of product information.

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WARNING: Bumex (bumetanide/Roche) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dosage schedule have to be adjusted to the individual patient's needs. (See under DOSAGE AND ADMINISTRATION in complete product information.)

INDICATIONS AND USAGE: Edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome.
Almost equal diuretic response occurs after oral and parenteral administration of Bumex. If impaired gastrointestinal absorption is suspected or oral administration is not practical, Bumex should be given by the intramuscular or intravenous route.
Successful treatment with Bumex following instances of allergic reactions to furosemide suggests a lack of cross-sensitivity.
CONTRAINDICATIONS: Anuria. Hypersensitivity and in patients in hepatic coma or in states of severe electrolyte depletion. Although Bumex can be used to induce diuresis in renal insufficiency, any marked increase in blood urea nitrogen or creatinine, or the development of oliguria during therapy of patients with progressive renal disease, is an indication for discontinuation of treatment.
WARNINGS: Dose should be adjusted to patient's needs. Excessive doses or too frequent administration can lead to profound water loss, electrolyte depletion, dehydration, reduction in blood volume and circulatory collapse with the possibility of vascular thrombosis and embolism, particularly in elderly patients.
Prevention of hypokalemia requires particular attention in patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis and ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, certain diarrheal states, or other states where hypokalemia is thought to represent particular added risk to the patients.
In patients with hepatic cirrhosis and ascites, sudden alterations of electrolyte balance may precipitate hepatic encephalopathy and coma. Treatment in such patients is best initiated in the hospital with small doses and careful monitoring of the patient's clinical status and electrolyte balance. Supplemental potassium and/or spironolactone may prevent hypokalemia and metabolic alkalosis in these patients.
In cats, dogs and guinea pigs, Bumex has been shown to produce ototoxicity. Since Bumex is about 40 to 60 times as potent as furosemide, it is anticipated that blood levels necessary to produce ototoxicity will rarely be achieved. The potential for ototoxicity increases with intravenous therapy, especially at high doses.
Patients allergic to sulfonamides may show hypersensitivity to Bumex.

PRECAUTIONS: Measure serum potassium periodically and add potassium supplements or potassium-sparing diuretics, if necessary. Periodic determinations of other electrolytes are advised in patients treated with high doses or for prolonged periods, particularly in those on low salt diets.
Hyperuricemia may occur. Reversible elevations of the BUN and creatinine may occur, especially with dehydration and in patients with renal insufficiency. Bumex may increase urinary calcium excretion.
Possibility of effect on glucose metabolism exists. Periodic determinations of blood sugar should be done, particularly in patients with diabetes or suspected latent diabetes.
Patients should be observed regularly for possible occurrence of blood dyscrasias, liver damage or idiosyncratic reactions.
Especially in presence of impaired renal function, use of parenterally administered Bumex should be avoided in patients to whom aminoglycoside antibiotics are also being given, except in life-threatening conditions.
Drugs with nephrotoxic potential and bumetanide should not be administered simultaneously.
Since lithium reduces renal clearance and adds a high risk of lithium toxicity, it should not be given with diuretics.
Probenecid should not be administered concurrently with Bumex.
Concurrent therapy with indomethacin not recommended.
Bumex may potentiate the effects of antihypertensive drugs, necessitating reduction in dosage.
Interaction studies in humans have shown no effect on digoxin blood levels.
Interaction studies in humans have shown Bumex to have no effect on warfarin metabolism or on plasma prothrombin activity.
Pregnancy: Bumex should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.
Bumetanide may be excreted in breast milk.
Pediatric Use: Safety and effectiveness below age 18 not established.
ADVERSE REACTIONS: Muscle cramps, dizziness, hypotension, headache and nausea, and encephalopathy (in patients with preexisting liver disease).
Less frequent clinical adverse reactions are weakness, impaired hearing, rash, pruritus, hives, electrocardiogram changes, abdominal pain, arthritic pain, musculoskeletal pain and vomiting.
Other clinical adverse reactions are vertigo, chest pain, ear discomfort, fatigue, dehydration, sweating, hyperventilation, dry mouth, upset stomach, renal failure, asterixis, itching, nipple tenderness, diarrhea, premature ejaculation and difficulty maintaining an erection.
Laboratory abnormalities reported are hyperuricemia, azotemia, hyperglycemia, increased serum creatinine, hypochloremia, hypokalemia, hyponatremia, and variations in CO_2 content, bicarbonate, phosphorus and calcium. Although manifestations of the pharmacologic action of Bumex, these conditions may become more pronounced by intensive therapy.
Diuresis induced by Bumex may also rarely be accompanied by changes in LDH, total serum bilirubin, serum proteins, SGOT, SGPT, alkaline phosphatase, cholesterol, creatinine clearance, deviations in hemoglobin, prothrombin time, hematocrit, platelet counts and differential counts. Increases in urinary glucose and urinary protein have also been seen.
DOSAGE AND ADMINISTRATION:
Oral Administration: The usual total daily dosage is 0.5 to 2.0 mg and in most patients is given as a single dose.
Parenteral Administration: Administer to patients (IV or IM) with GI absorption problem or who cannot take oral. The usual initial dose is 0.5 to 1 mg given over 1 to 2 minutes. If insufficient response, a second or third dose may be given at 2 to 3 hour intervals up to a maximum of 10 mg a day.
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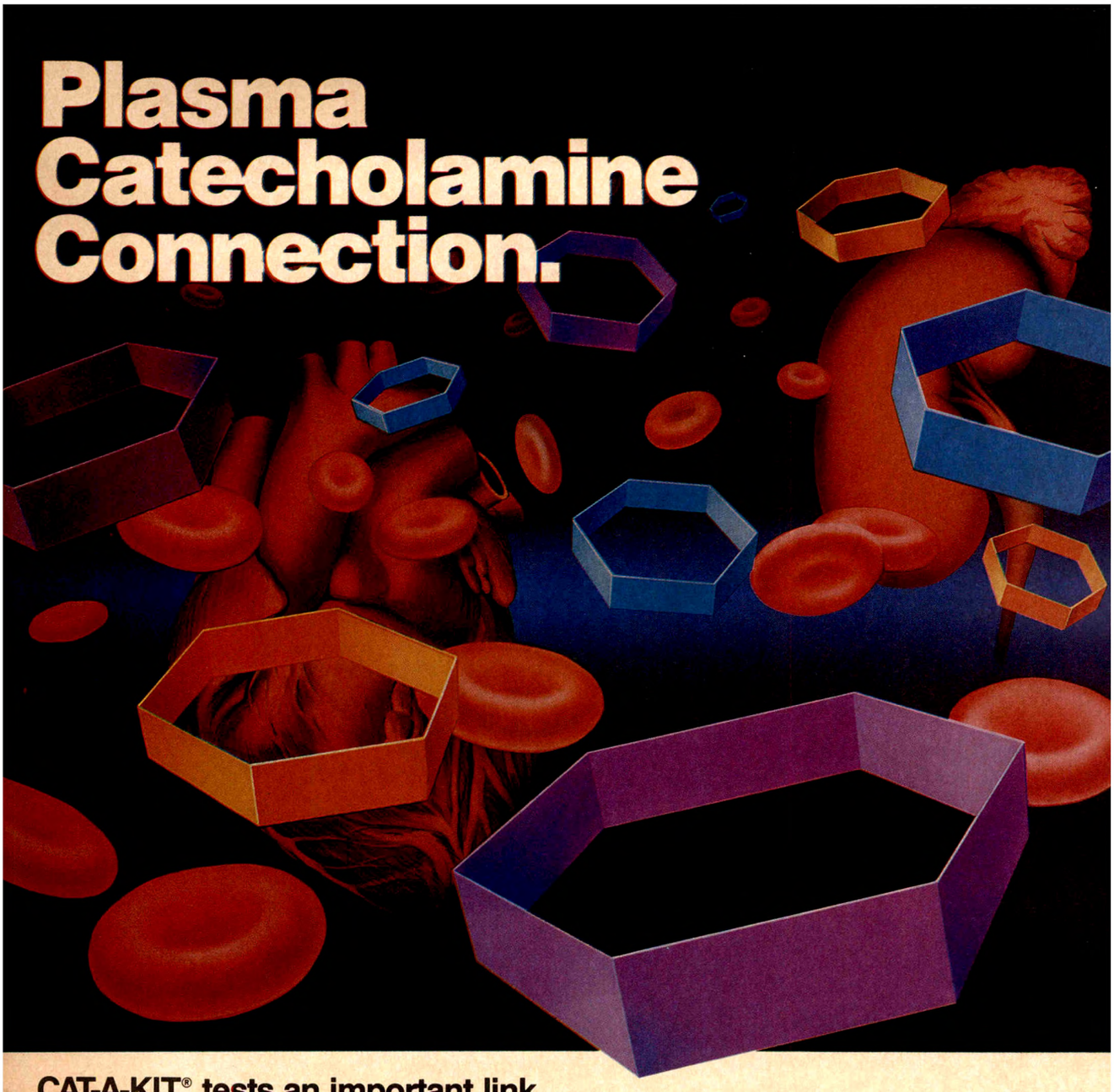

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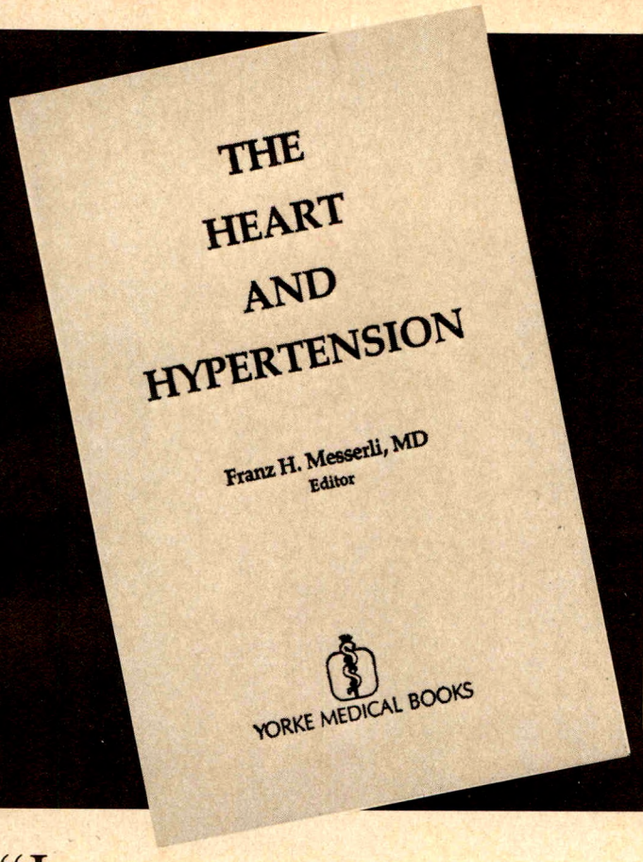

The Heart and Hypertension

Franz H. Messerli, MD, Editor

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Part II
Epidemiology of Left Ventricular Hypertrophy

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Morphology and Biochemical Changes

Part IV
Pathophysiology of Left Ventricular Hypertrophy

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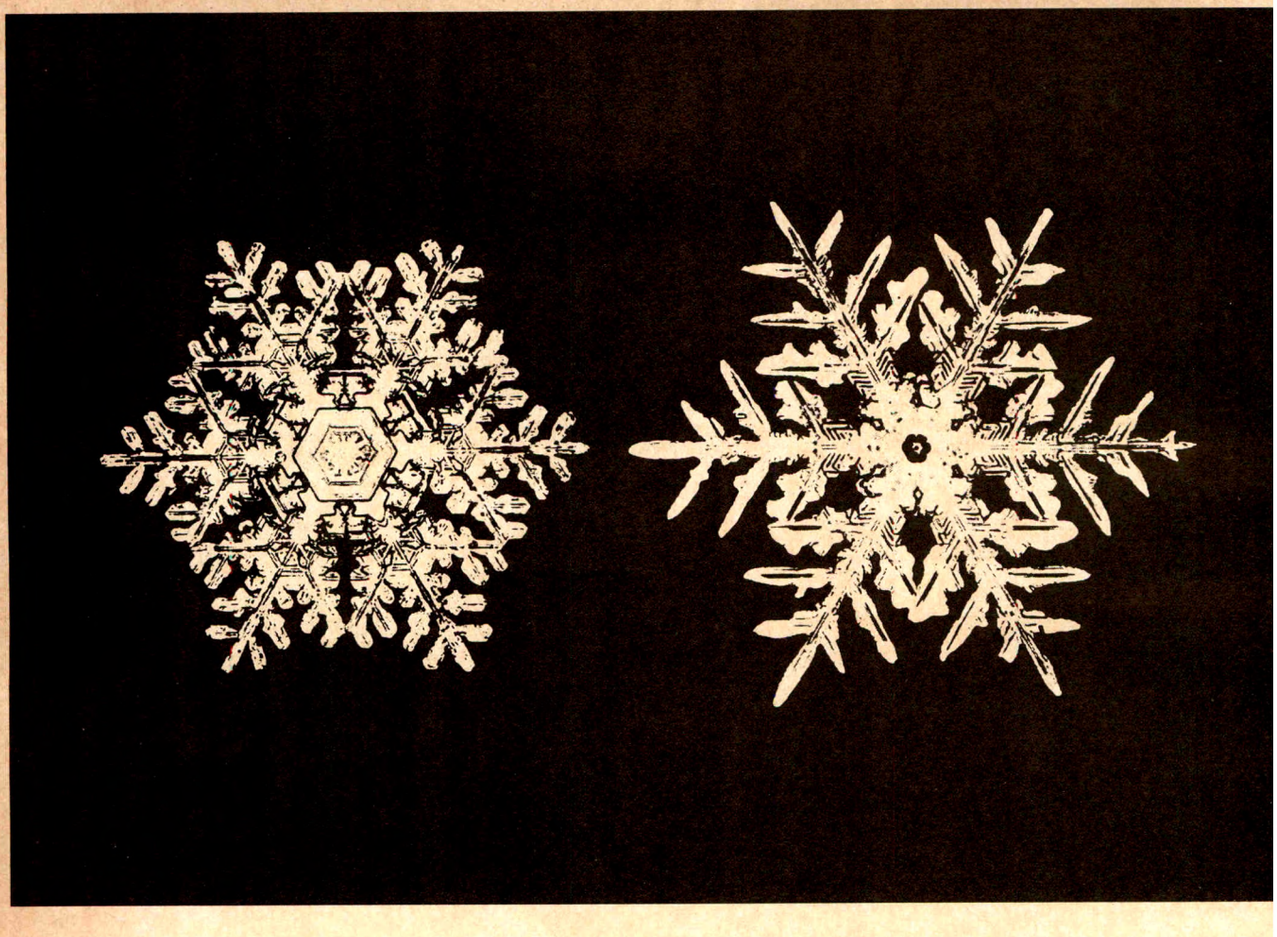

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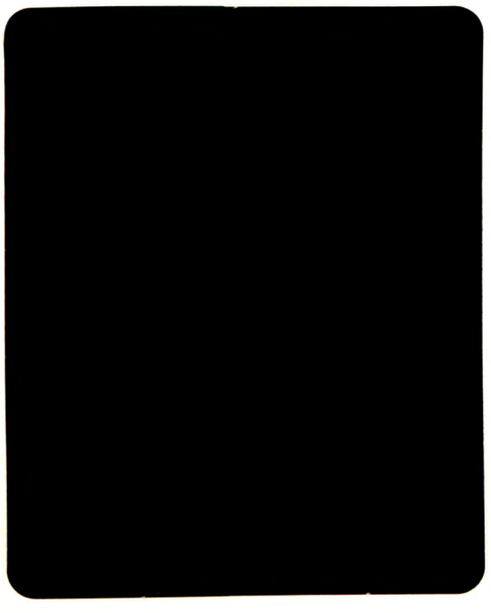
You know how important it is for your MI/TIA patients to adhere to a prescribed regimen of daily low-dose aspirin. Recent long-term studies on aspirin therapy for prevention of stroke or MI indicate that one regular-strength aspirin per day provides comparable antiplatelet effects to approximately four aspirin tablets per day but with reduced risk of GI side effects.[1-4]



But what might happen when your MI/TIA patient uses additional aspirin for pain relief when he or she has a headache or a cold or flu? Prophylactic therapy for MI/TIA may be compromised by the increased risk of GI side effects when your patient takes additional aspirin for other reasons.

Studies have shown that even routine doses of aspirin can cause GI side effects. Aspirin-associated dyspepsia has been estimated to occur in 5% to 25% of all aspirin users. And endoscopic studies in healthy volunteers demonstrate that analgesic doses of aspirin can result in GI erosions, ulcerations, and submucosal hemorrhage.[5-7]

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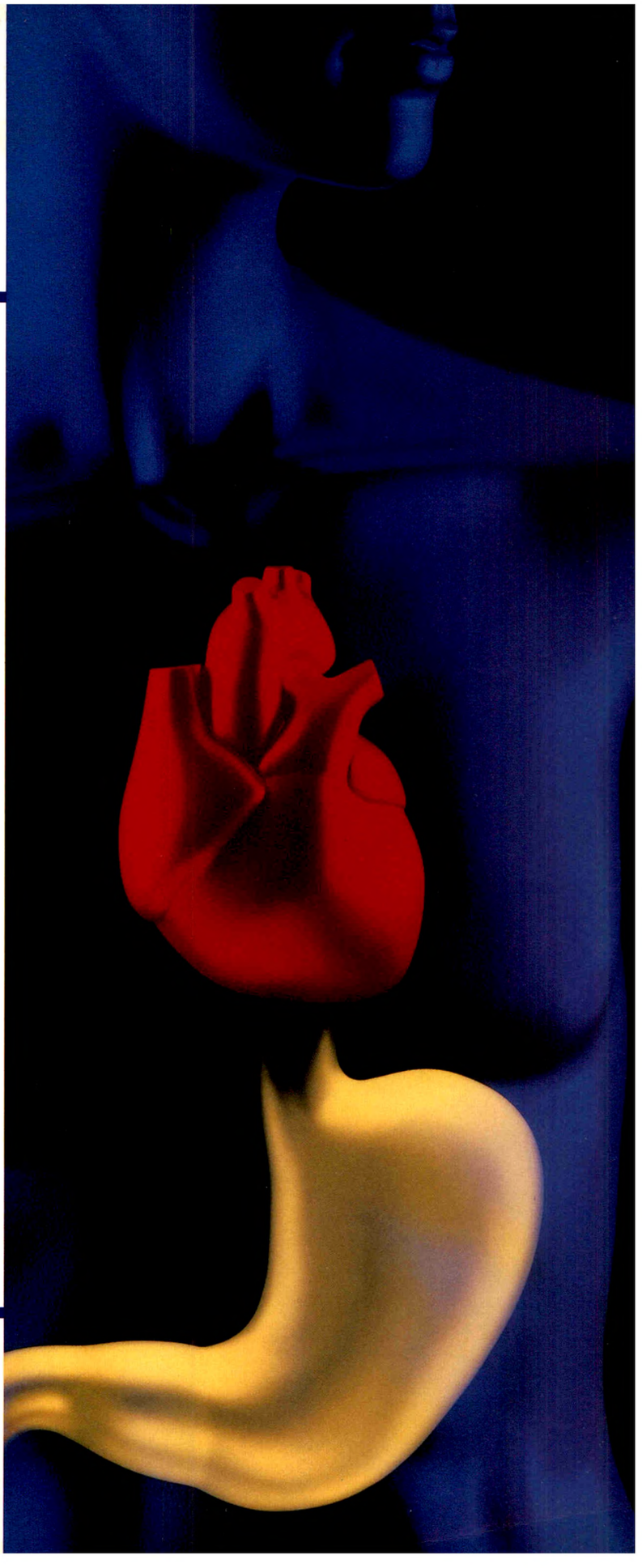

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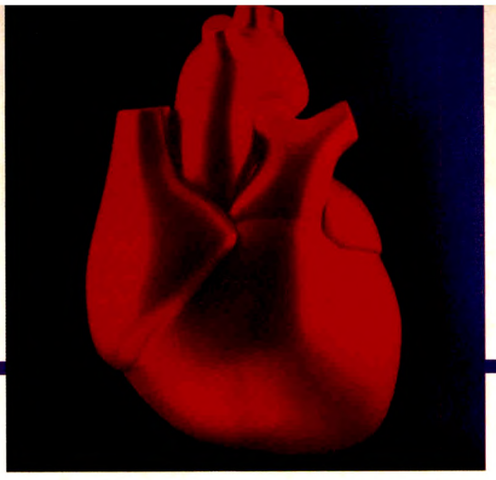

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An Echocardiographic Study of the Association of Ventricular Septal Defect and Right Ventricular Muscle Bundles with a Fixed Subaortic Abnormality

MICHAEL VOGEL, MD, JEFFREY F. SMALLHORN, BS, MB, ROBERT M. FREEDOM, MD, JOHN COLES, MD, WILLIAM G. WILLIAMS, MD, and GEORGE A. TRUSLER, MD

Since 1983, 36 patients with the combination of right ventricular muscle bundles and a perimembranous ventricular septal defect have been studied in our institution to address the incidence of an associated subaortic abnormality. Of that total 32 (88%) had echocardiographic evidence of such an abnormality (29 had a typical subaortic ridge protruding from the crest of the interventricular septum and the remaining 3 had an echodense area in the same location). Surgical confirmation of the presence or absence of a subaortic abnormality was available in 26. There was correlation between the surgical and echocardiographic findings in all patients. A resting Doppler gradient of ≥10 mm Hg was present in only 10. During the study period, 6 patients had Doppler evidence of progression of their gradient. The incidence of subaortic abnormalities in right ventricular muscle bundles and ventricular septal defects appears to be far greater than previously suspected. The exact significance of this finding in the absence of a pressure gradient is still unclear.

(Am J Cardiol 1988;61:857–860)

The combination of ventricular septal defect (VSD), anomalous right ventricular (RV) muscle bundles and a fixed subaortic abnormality has previously been described.[1–3] What is less clear is the incidence of a subaortic abnormality in the setting of RV muscle bundles and a VSD. This stems from the fact that previous studies have been based on angiographic evaluation, which is known to underestimate the presence of a subaortic abnormality in the setting of a VSD.[4] Cross-sectional echocardiography, on the other hand, provides a detailed assessment of the subaortic region, independently of the presence or absence of a VSD.[4–6] This study addresses the frequency of a subaortic abnormality in patients with VSD and RV muscle bundles as assessed by cross-sectional echocardiography.

From the Departments of Pediatrics and Surgery, Division of Cardiology and Cardiovascular Surgery, Faculty of Medicine, University of Toronto, and the Departments of Pediatrics and Surgery, The Hospital for Sick Children, Toronto, Ontario, Canada. Dr. Vogel's work was supported by grant Vo390/01 from the Deutsche Forschungsgemeinschaft, Bonn, West Germany. Manuscript received July 8, 1987; revised manuscript received and accepted December 10, 1987.

Address for reprints: J.F. Smallhorn, MD, Division of Cardiology, Hospital for Sick Children, 555 University Avenue, Toronto M5G 1X8, Canada.

Methods

Only patients with the combination of a perimembranous VSD and anomalous RV muscle bundles were included. Although patients with typical anatomy of tetralogy of Fallot[7] may occasionally have an associated subaortic abnormality (the incidence at our institution being 0.7%), we arbitrarily chose to exclude them from this study.

Definitions: The diagnosis of either anomalous RV muscle bundles or a subaortic abnormality does not depend on a recorded pressure gradient across the right or left ventricular overflow tracts, respectively. For this reason, the term obstruction or stenosis has not been employed, but rather the term subaortic abnormality. We are aware that there is considerable morphological overlap between the various abnormalities encountered in the left ventricular outflow tract.[8]

Echocardiographic evidence of a subaortic abnormality was defined either as a typical subaortic ridge seen in the parasternal long- and short-axis views,

TABLE I Age and Pressure Gradient Across the Left Ventricular Outflow Tract in 6 Patients with Increase Doppler Gradient

Pt	Age (mo)		Pressure Gradient (mm Hg)	
	First Study	Second Study	First Study	Second Study
1	4	24	10	20
2	82	94	0	10
3	15	26	0	20
4	36	47	0	16
5	2	36	0	16
6	10	19	0	10

originating from the crest of the ventricular septum and protruding at right angles to the endocardial surface, with or without extension to the anterior mitral valve leaflet (Figure 1), or as an abnormal echodense area on the crest of the ventricular septum, seen in both the parasternal long- and short-axis views.

Owing to potential problems of differentiating specular reflections from a minor subaortic abnormality, we chose to examine the interobserver variant. Each of the 2 observers, independently and without prior knowledge of the diagnosis, reviewed 10 echocardiographic studies of patients with VSD and RV muscle bundles who had surgical confirmation of a subaortic abnormality, and also 10 studies from patients with an isolated VSD who also had undergone surgical repair.

In addition, there is considerable heterogeneity among the muscular structures resulting in the so-called double-chambered right ventricle.[9,10] The anomalous RV muscle bundles producing obstruction in the right ventricle may be considered abnormally positioned and hypertrophied septoparietal trabeculations.[10]

Anomalous RV muscle bundles assessed echocardiographically were defined as echodense structures protruding at right angles to the infundibular septum and RV free wall.[11] As a result, the right ventricle was divided into an upper chamber communicating with the pulmonary artery and a lower chamber connecting with the VSD and the inlet portion of the right ventricle.[10]

Echocardiographic technique: The echocardiographic examinations were performed using commercially available equipment. Imaging was carried out with either a 3.5-, 5- or 7.5-MHz transducer, depending on the size of the patient. The studies were recorded on either a 3/4- or 1/2-inch video display system with slow motion or single-frame analysis capability. Restless patients were sedated with chloral hydrate for the echocardiographic examination.

All studies were performed in a standard fashion by either 1 of 3 echocardiographic technicians. The left and right ventricular outflow tracts were evaluated in the standard long-axis views. In the standard parasternal short-axis view, the subaortic area was visualized just beneath the right aortic cusp in a scan from apex to base. In this view, the relation between the subaortic abnormality and the anomalous RV muscle bundles could be determined.

The subaortic region also was assessed from the subcostal long-axis view of the left ventricular outflow tract. From this view the transducer was then rotated clockwise and the right ventricular outflow imaged in its long axis for a demonstration of the right ventricular muscle bundles.[11]

Doppler interrogation of the left ventricular outflow tract was performed from the suprasternal and the apical 5-chamber view. Doppler scanning of the RV outflow tract was performed in the subcostal long-axis view. This position is superior to the parasternal short-axis view as the Doppler beam can be aligned parallel to the direction of blood flow.

Although the modified Bernoulli equation ($p = 4\ v^2$) was used to calculate gradients across the left and right ventricular outflow tract,[12] we were aware of its limitations when evaluating mild obstruction. As a result, a gradient of $\geq$10 mm Hg was considered to be abnormal if there was associated evidence of disturbed flow by Doppler. Serial Doppler evaluation of the left ventricular outflow tract has thus far been performed in 19 patients.

To determine whether the association of VSD and RV muscle bundles with a subaortic abnormality was due to more than just chance, the incidence of each abnormality alone was determined from our cardiac data center for the same time period. These incidences were then compared with the 2 lesions combined.

Patient population: Between January 1983 and May 1987, 36 consecutive patients with an echocardiographic diagnosis of perimembranous VSD and RV muscle bundles were identified. These patients were not preselected, being routine cases referred to the echocardiographic laboratory for evaluation. All patients had concordant atrioventricular and ventriculoarterial connections. The mean age of the group was 2.4 $\pm$ 2.5 years (1 week to 11 years). The male to female ratio was 3:1.

Results

Incidence of an associated subaortic abnormality: During the study period 11,300 patients were evaluated in the cardiology department. Of those, 36 were found to have a VSD and RV muscle bundles and 91 a diagnosis of fibromuscular subaortic stenosis (the diagnosis used in our current coding system). Therefore, the highest possible incidence of the association between these lesions by chance would be 8.5%, which in reality is far less than the observed value of 86% ($p < 0.001$).

Of the total group, 32 (88%) had either a typical subaortic shelf (29 of 32) or an abnormal echodense area (3 of 32) on the crest of the ventricular septum. A subaortic abnormality has been resected in 22 of the 26 patients, who have thus far undergone surgical repair of their lesion. Of these 22 patients, 20 had a typical shelf whereas the other 2 had an echodense area on the crest of the septum. In the remaining 4 patients, 3 had no evidence of an associated subaortic abnormality and 1 had a small ridge of fibrous tissue that the

surgeons could not resect through the VSD (this was one of our earlier cases and at that time it was elected not to open the aortic root).

The youngest patient identified with a subaortic abnormality in the setting of VSD and RV muscle bundles was a premature baby (35-week gestation) studied at 1 week of age.

Each of the 2 independent observers correctly identified those 10 patients with an abnormal subaortic area in association with a VSD and RV muscle bundles from the 10 patients with a VSD alone and a normal left ventricular outflow tract. Among the 10 patients presented for interobserver variability, 3 had an abnormal echodense area on the crest of the ventricular septum.

Although the subaortic abnormality was observed in every patient, the parasternal short-axis view appeared to be the best position for identifying it. From the parasternal long-axis view the abnormality could be seen in all but 3, whereas the subcostal long-axis view failed to identify it in 8 patients. Interestingly, the subaortic abnormality and the RV muscle bundles appeared to lie in the same plane when imaged in the precordial short-axis view.

Doppler evaluation: The combination of a gradient across the left ventricular outflow tract of ≥10 mm Hg and Doppler evidence of turbulent flow was observed in 10 patients at their last echocardiographic examination. The gradients ranged from 10 to 20, with a mean of 15 ± 4 mm Hg. Of those 19 who had undergone serial Doppler interrogation of the left ventricular outflow tract, progression of the pressure gradient was documented in 6 (29%). These data are summarized in Table I. The heart rate at the first study was 127 ± 15 and 105 ± 10 beats/min at the second ($p < 0.01$).

The VSD, located in the perimembranous region in all patients, was restrictive by Doppler criteria in 10, with spontaneous closure throughout the study period observed in 1 patient. There appeared to be a degree of septal malalignment between the infundibular and trabecular septum in all patients, with the infundibular septum being displaced slightly anteriorly (Figure 1).

Morphologic description of right ventrciular muscle bundles: At surgery, the right atrium was opened and the right ventricular cavity inspected through the tricuspid valve. In all cases, an obstructive hypertrophied septoparietal muscle bar was found. The tricuspid valve had attachments to this hypertrophied band in 5 patients and an abnormally placed papillary muscle of the tricuspid valve contributed to the obstruction in 1.

Discussion

Incidence of a subaortic abnormality: It would appear from our data that the incidence of a subaortic abnormality is far greater than previously reported.[1,3] This is most likely related to previous difficulties in identifying a subaortic abnormality by angiocardiography in the setting of a VSD, particularly when there is no pressure gradient across the left ventricular outflow tract.[4]

Our data would suggest that at the time of diagnosis the majority of patients do not have evidence of hemodynamic obstruction. This raises the issue of the significance of the subaortic abnormality. Certainly, if there is a resting gradient, it would seem advisable to resect the subaortic abnormality at the time of VSD closure and RV muscle bundle resection. In the absence of a resting gradient, if the abnormality is not removed, there is a potential for progression.[13-15] As the frequency and rate of progression are still unclear,[15,16] it would seem prudent to remove the abnormality because this could potentially avoid reoperation at a later stage.

Identification of a subaortic abnormality: From our data it would appear that observer variability did not play a part in the echocardiographic diagnosis of a

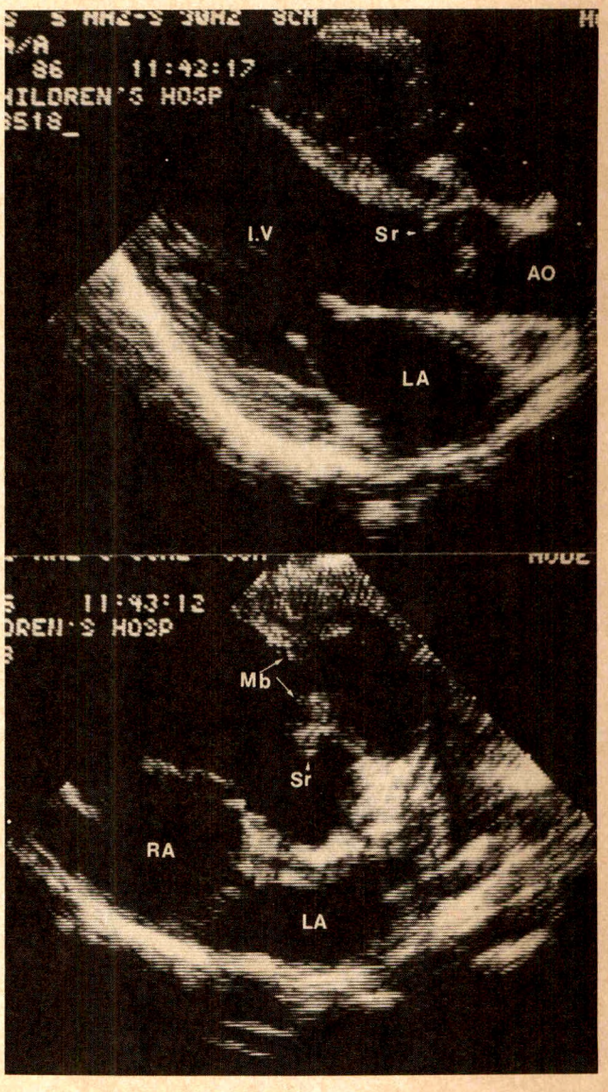

FIGURE 1. Typical subaortic ridge (Sr) protruding at right angles to the endocardial surface. The parasternal short-axis view shows both the RV muscle bundle and the subaortic ridge. AO = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricular.

subaortic abnormality. This in part may be related to reliance on 2 imaging planes in most patients. Although those patients with a tyical subaortic shelf are straightforward from the diagnostic standpoint, we are aware that patients with an echodense area on the crest of the ventricular septum may be difficult to differentiate from specular reflections or the so-called T artifact.[17] In such a situation, careful serial assessment may shed light on the issue. Thus far, however, even these patients (who have been put forward for surgery) have had abnormal subaortic tissue resected.

Relation between right ventricular muscle bundles and a subaortic abnormality: The other interesting aspect of this study is the close relation between the anamalous RV muscle bundles and the subaortic abnormality. Whereas it might be tempting to speculate that these 2 lesions are predicated on the same myocardial abnormality, we have no histologic data to support this.

Although evidence would suggest that the muscle bundles are congenital[10] and the subaortic abnormality acquired,[15] the patient who was 1 week of age and premature at the time of diagnosis might lend some support to the argument that this is possibly a congenital lesion.[18] Certainly, the positive aspect of this relation lies in the ease of the diagnosis by cross-sectional echocardiography.

Finally, the VSD was similar to that described by previous investigators, with associated malalignment between the trabecular and infundibular septum.[19] It has been postulated that this septal malalignment may play a role in the pathogenesis of subaortic stenosis.[19] Of note is that, despite this anterior malalignment of the infundibular septum, these patients are clearly different from those with tetralogy of Fallot.

In conclusion, there appears to be a higher than previously suspected incidence of subaortic abnormalities in perimembranous VSD and RV muscle bundles. The exact significance of this, in the absence of a measurable pressure gradient, is still unclear, although data would suggest progression in some cases. For this reason, our current policy is to resect this abnormality at the time of surgical correction of the associated lesions.

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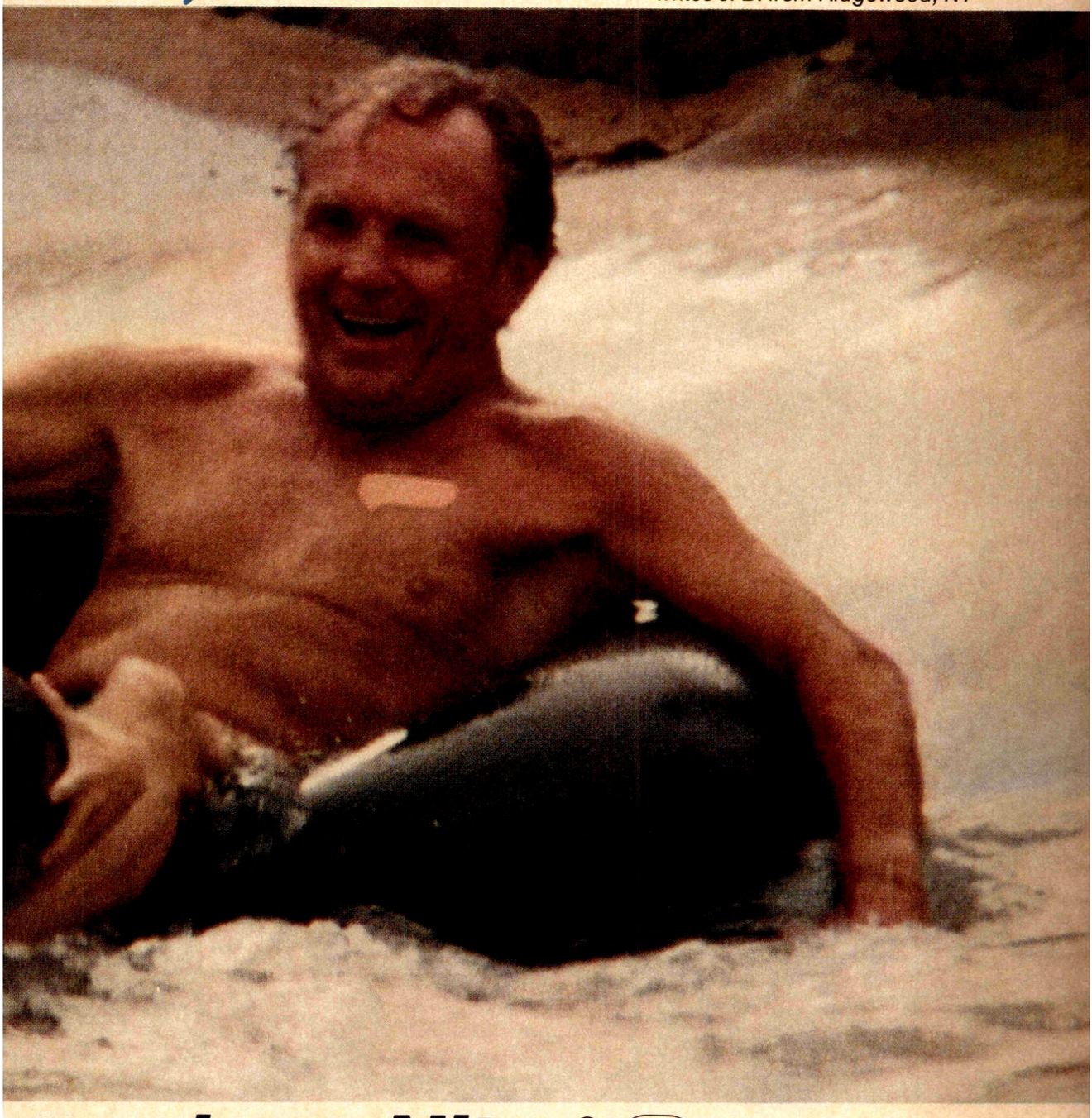

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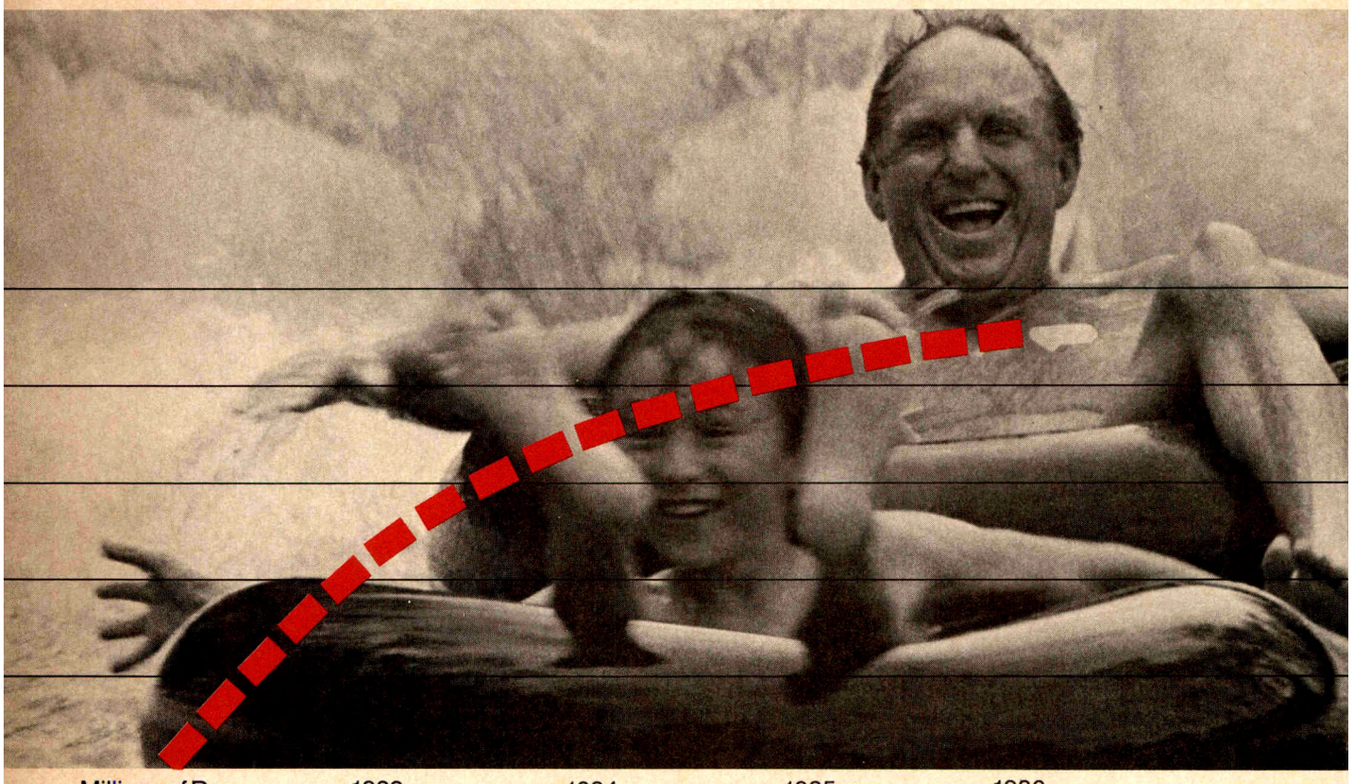

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Cardiorespiratory Exercise Testing After Venous Switch Operation in Children with Complete Transposition of the Great Arteries

TONY REYBROUCK, DSc, MONIQUE DUMOULIN, MD,
and LUCAS G. VAN DER HAUWAERT, MD

In 14 children who underwent a venous switch operation for complete transposition of the great arteries, exercise testing was performed 3 to 15 years (mean 8) after the operation. Exercise performance capacity was assessed by the determination of the ventilatory threshold during exercise and by the oxygen uptake ($\dot{V}O_2$) reached at a heart rate of 170 beats/min ($\dot{V}O_2$,170). The ventilatory threshold was defined as the highest oxygen uptake ($\dot{V}O_2$) at which the pulmonary ventilation ($\dot{V}_E$) stops to increase linearly when related to $\dot{V}O_2$. During exercise above this threshold a disproportionate increase in $\dot{V}_E$ relative to $\dot{V}O_2$ is observed. The mean ventilatory threshold was significantly lower ($p < 0.01$) than the normal mean value and averaged 72 ± 15%, 67 ± 15% and 70 ± 13% of the predicted normal value for children of comparable age, weight and height, respectively. The mean value for $\dot{V}O_2$,170 also was significantly lower ($p < 0.05$) than the normal mean value for children of comparable age, weight and height, and averaged 81 ± 20%, 81 ± 18% and 80 ± 18%, respectively. Compared with normal control subjects of the same sex and age, the ventilatory threshold was surpassed sooner ($p < 0.001$) and reached after 2 ± 1 min instead of the 4 ± 1 min required by the controls. In nearly half of the patients, a lower than normal (i.e. below the 95% confidence limit) heart rate response to exercise was observed. Theoretically, this could be interpreted as indicating a normal or high physical performance capacity. However, the ventilatory threshold was subnormal in all but 1 of these patients. The blunted heart rate response observed in many patients after a venous switch operation suggests sinoatrial dysfunction secondary to extensive intraatrial operation.

(Am J Cardiol 1988;61:861–865)

After a venous switch operation, most patients with transposition of the great arteries (TGA) function normally and are clinically well. However, because the right ventricle has to cope with systemic pressures and right ventricular dysfunction has been frequently documented,[1–5] it may be questioned whether these patients have the same exercise capacity as their healthy peers. In patients operated for TGA, only limited information is available on maximal exercise performance assessed by maximal endurance time on a treadmill,[3,6–8] maximal workload on a bicycle ergometer[2,4] or maximal oxygen uptake.[7] To our knowledge, no data are available on gas exchange during submaximal exercise. The purpose of our study was to measure respiratory gas exchange during graded submaximal exercise and thus determine the ventilatory threshold, defined as the highest oxygen uptake ($\dot{V}O_2$) at which pulmonary ventilation ($\dot{V}_E$) stops to increase linearly with increasing $\dot{V}O_2$.[9,10] Above this exercise intensity a disproportionate increase in $\dot{V}_E$ relative to $\dot{V}O_2$ is observed. Because heart rate response during exercise still is widely used in the assessment of cardiorespiratory performance capacity, it also was evaluated in our study.

From the Departments of Pediatric Cardiology and Cardiovascular Rehabilitation, Gasthuisberg University Hospital, University of Leuven, Belgium. Manuscript received July 24, 1987; revised manuscript received and accepted November 23, 1987.

Address for reprints: Lucas G. Van der Hauwaert, MD, Department of Pediatric Cardiology, Gasthuisberg University Hospital, 3000 Leuven, Belgium.

Methods

Patients: From 1980 to 1986, 14 asymptomatic patients (9 boys and 5 girls) with regular sinus rhythm were selected from a larger group of TGA patients to undergo graded exercise testing on a treadmill, 3 to 15

TABLE I Anthropometrical and Clinical Characteristics of the Patients

Pt	Age at Testing (yrs), Sex	Age at Surgery (mo)	Type of Surgery	Interval Between Exercise Testing and Surgery (yrs)	Weight (kg)	Height (cm)
1	6, F	3	MO	6	21	118
2	13, F	38	MO	10	45	157
3	8, M	23	MO	6	21	115
4	11, F	23	MO	9	31	114
5	6, M	19	MO	5	20	122
6	4, M	12	SO	3	15	95
7	12, M	12	MO	11	34	147
8	7, M	18	SO	6	22	124
9	10, M	21	MO	9	26	133
10	5, M	11	SO	4	17	110
11	8, F	18	MO	6	24	131
12	16, M	51	MO	12	46	173
13	8, F	15	MO	7	23	126
14	18, M	41	MO	15	73	167

MO = Mustard operation; SO = Senning operation.

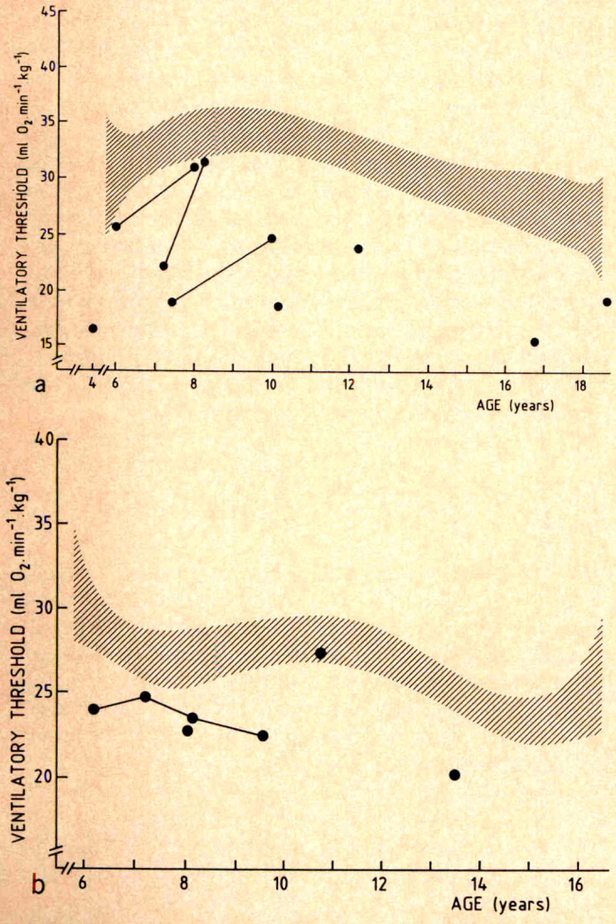

FIGURE 1. Individual values for ventilatory threshold in 8 boys (*A*) and 4 girls (*B*) operated on for transposition of the great arteries. The 95% confidence limits of the normal value are shown by the shaded area. For patients in whom repeated exercise studies were available, the dots are connected with a line.

years (mean 8 ± 3 standard deviation) after a venous switch operation. Children <4 years and patients with overt sinoatrial node dysfunction, hemodynamically important associated lesions, gross cardiomegaly or mental retardation were excluded. The pertinent clinical data are listed in Table I.

The age at correction varied from 3 to 51 months (mean 22 ± 13). The Mustard operation was performed in 11 patients and the Senning procedure in 3. All patients were asymptomatic at the time of investigation. None was taking medication. The interval between operation and exercise testing varied from 3 to 15 years (mean 8 ± 3). In 4 patients, exercise testing was repeated 5 months to 2.4 years after the initial assessment. The overall result of surgery in this selected group was considered to be "excellent." Age, at the time of the exercise test, varied from 4 to 19 years (mean 9 ± 4), body weight ranged from 15 to 73 kg (mean 30 ± 16) and body height from 95 to 173 cm (mean 131 ± 23). When the data for height and weight were expressed as percentiles,[11] 1 out of 14 patients was below the third percentile for weight and 3 of 14 were below it for height.

Testing procedures: The methods used have already been reported in detail.[12–14] Briefly, graded exercise testing was performed on a treadmill. The speed of the treadmill was set at 4.8 km/hr and 5.6 km/hr for children below and above 6 years of age, respectively.[15] The inclination was increased stepwise by 2% every minute until a heart rate of 170 beats/min was reached. The electrocardiogram from a biopolar lead was continuously monitored.

Oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$) were measured by the Douglas bag method. Exercise performance was assessed by determination of the ventilatory threshold, expressed in ml O_2/min/kg and in units of time (min). The ventilatory threshold was determined as the exercise intensity at which a continuous increase was found for the ventilatory equivalent for O_2 ($\dot{V}_E/\dot{V}O_2$) without a concomitant increase in the ventilatory equivalent for CO_2 ($\dot{V}_E/\dot{V}CO_2$).[12,16] Furthermore, the exercise intensity or $\dot{V}O_2$ reached at a heart rate of 170 beats/min ($\dot{V}O_2$,170) was determined and heart rate response assessed during submaximal exercise at various inclinations of the treadmill. Heart rate, expressed as a percentage of the mean normal value, was considered to be subnormal when it fell below the 95% confidence limit.[17] The values for ventilatory threshold and $\dot{V}O_2$,170 in these patients were compared with the values obtained in 234 age-matched healthy children.[12]

Differences between mean values were calculated by analysis of variance. For correlation analysis, the Pearson correlation method was used. The dispersion of the data is given by the standard deviation of the mean and for normal children also by the 95% confidence limits.

Results

Exercise performance: The ventilatory threshold could be determined in 12 of 14 patients. Individual

TABLE II Characteristics of Aerobic Function During Exercise in 14 Patients Operated for Transposition of the Great Arteries

Pt	VT (ml O_2/min/kg)	VT Age Pred (%)	VT Weight Pred (%)	VT Height Pred (%)	VO_2, 170 (ml O_2/min/kg)	$\dot{V}O_2$, 170 Age Pred (%)	$\dot{V}O_2$, 170 Weight Pred (%)	$\dot{V}O_2$, 170 Height Pred (%)
1	24	82	77	84	26	92	85	91
2	20	81	76	79	24	94	91	89
3	18	56	55	60	29	85	87	83
4	27	97	98	91	31	106	112	106
5	25	83	76	78	—	—	—	—
6	16	54	54	54	26	69	69	69
7	23	73	68	72	36	108	102	105
8	22	67	65	66	20	60	61	61
9	18	53	53	54	23	67	67	68
10	—	—	—	—	34	109	102	95
11	23	85	79	81	26	92	89	90
12	15	56	47	54	23	63	71	64
13	—	—	—	—	18	65	60	63
14	19	75	60	64	19	49	58	54

Pred = predicted; $\dot{V}O_2$,170 = oxygen uptake at a heart rate of 170 beats/min; VT = ventilatory threshold.

results are listed in Table II and Figure 1A and B. In 11 of these patients, the ventilatory threshold was below the 95% confidence limit obtained in normal children of comparable age. The mean value for the ventilatory threshold was significantly lower ($p < 0.01$) than the normal value, averaging 72 ± 15%, 67 ± 15% and 70 ± 13% of the normal mean value obtained in children of the same sex and of comparable age, weight or height, respectively. In 11 patients the ventilatory threshold was attained sooner than in normal controls and in 3 patients it was already surpassed at the start of the exercise test. When expressed in units of time, the ventilatory threshold was reached after 2.2 ± 1.2 minutes in the patients and after 4.0 ± 1.1 in normal children of the same sex and comparable age. The difference was statistically significant ($p < 0.01$).

In the 4 patients in whom the exercise test was repeated, the ventilatory threshold remained subnormal at the second assessment (Figure 1A and B). When expressed as a percentage of the age-predicted normal value, the ventilatory threshold averaged 72 ± 13% at the first evaluation and 85 ± 10% at the second evaluation.

The $\dot{V}O_2$ reached at a heart rate of 170 beats/min ($\dot{V}O_2$,170) was subnormal and averaged 81 ± 20%, 81 ± 18% and 80 ± 18% of the normal mean value obtained in children of the same sex and of comparable age, weight and height, respectively. The difference between normal subjects and patients was statistically significant ($p < 0.05$).

Heart rate response during graded exercise: Heart rate response could be studied throughout several exercise levels in 13 of the 14 patients (Figure 2). When expressed as a percentage of the age-predicted normal value, a subnormal value (below the 95% confidence limit for at least 2 exercise levels) was observed in 5 of these patients. In 4 of them, a subnormal value for ventilatory threshold was found. Of the remaining 8 patients, 4 had a normal heart rate response (between the 95% confidence limits) and 4 a heart rate response above the 95% confidence limit. In these 8 patients the ventilatory threshold was subnormal. Thus, no relation was found between ventilatory threshold and heart rate response. During exercise and during the immediate recovery period, premature atrial beats were recorded in 4 patients. In another patient, both premature atrial and ventricular beats and couplets were observed during and immediately after exercise.

Exercise performance and clinical data: No relation was found in this small series of patients between the age at surgery and the ventilatory threshold expressed as a percent of the predicted normal value for children of the same age ($r = 0.28$), weight ($r = 0.18$) and height ($r = 0.14$). Neither was there a significant relation between the exercise performance capacity (% of normal) and the time lapse between surgery and the exercise test ($r = 0.07$ for age, $r = -0.13$ for weight and $r = -0.08$ for height-predicted normal value).

Discussion

Despite the absence of clinical symptoms and the fact that all patients were normally attending school and took part in games, most showed a subnormal exercise tolerance when assessed by the ventilatory threshold method. Poor exercise tolerance has previously been reported in a considerable number of patients who underwent a Mustard or Senning operation for TGA.[4,6,8,18,19] The comparison of these studies is difficult because different methods for evaluating exercise performance were used: $\dot{V}O_2$max,[18] maximal endurance time on the treadmill[6,8,19] or maximal workload on the bicycle ergometer.[2] Also, different criteria for normality were applied, that is, maximal treadmill time <8 minutes,[18] $\dot{V}O_2$max <40 ml/min/kg[18] and 1 standard deviation below the mean normal value for maximal endurance time on the treadmill.[6,8,19]

Our observation that a larger fraction of patients had subnormal values for exercise performance than

noted in previous studies may be explained by the sensitivity of the method we elected to use. In previous investigations on cardiorespiratory endurance capacity in children with congenital heart disease and left-to-right shunt[13] and in children operated on for tetralogy of Fallot[14] it has been shown that the ventilatory threshold method is more sensitive to detect subnormal exercise capacity than other indexes of cardiorespiratory performance capacity such as $\dot{V}O_2$,170, $\dot{V}O_2$max[20] or the maximal endurance time on a treadmill.[21] A considerable advantage of the ventilatory threshold measurement is its independence of the child's motivation to perform a maximal effort as required in the Bruce treadmill protocol. Furthermore, when repeated within a time interval of 1 to 3 years after the initial testing, we found the measurements to be reproducible (Figure 1A and B). This confirms the results of Lipkin et al,[22] who found reproducible results in a group of adults with impaired ventricular function who underwent at least 3 exercise tests over 2 to 14 days. Although the ventilatory (anaerobic) threshold was originally defined as the exercise intensity or $\dot{V}O_2$ at which a concomitant disproportionate increase in $\dot{V}_E$ and lactate occurred relative to $\dot{V}O_2$,[9,23] we have been using this index of exercise performance in a pragmatic way, without implying a causal relationship with the onset of metabolic acidosis during graded exercise.

Subnormal exercise performance in patients after venous switch operations for TGA has generally been attributed to dysfunction of the right (systemic) ventricle,[1-5] as demonstrated by a depressed right ventricular ejection fraction,[24-26] failure to increase the right ventricular ejection fraction or stroke volume during exercise[2-5] or an increased right ventricular end-diastolic volume.[1,24,25] It has been suggested that the intrinsic geometry and fiber array of the right ventricle make it less suitable to function as a systemic pump.[25,27] Our findings, which indicate a reduced exercise performance and a lowered ventilatory threshold in the majority of patients, are in accordance with these hemodynamic studies.

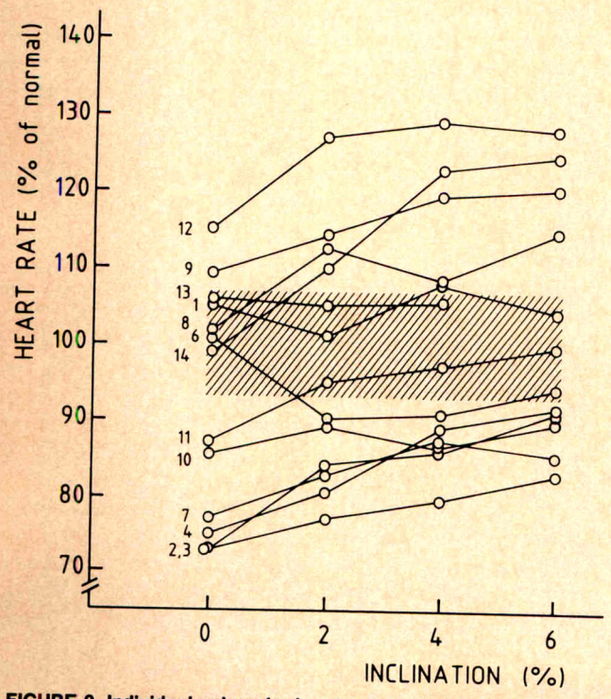

FIGURE 2. Individual values for heart rate response during graded treadmill exercise. The 95% confidence limits of the normal value are shown by the shaded area. The numbers refer to the patient numbers listed in Table I.

Another contributing factor to the reduction of exercise performance is the impaired chronotropic reserve. In patients operated for TGA, heart rate response to maximal exercise has been shown to be significantly reduced.[5-7,18,19] Therefore, when these patients undergo a given exercise, their heart rates should be considered to represent a higher percentage of the maximal exercise capacity than is the case in normal subjects. This is confirmed by the fact that TGA-operated patients experience an exercise at a heart rate of 170 beats/min as being close to their maximal capacity, whereas normal children will perceive it as only moderately heavy. In the present study, based on submaximal exercise, a lower than normal heart rate response was found in nearly half of the patients. Theoretically, a low or normal heart rate response during exercise—as observed in endurance-trained individuals—should be associated with a high or normal value for ventilatory threshold or maximal oxygen uptake. However, in our patients there was no relation between heart rate response and ventilatory threshold, which illustrates the fact that the latter, a parameter of aerobic function, is independent of heart rate response. This is also confirmed by the lower mean value for ventilatory threshold (72 ± 15%) expressed as a percentage of the age-predicted normal value, compared to the mean value for $\dot{V}O_2$,170 (81 ± 20%). In previous studies, a blunted heart rate response during submaximal exercise has been attributed to sinoatrial node dysfunction after intraatrial operation.[6,28]

At variance with other studies[6,18,28] in which multifocal ventricular premature beats, sinus node dysfunction and atrioventricular block were recorded during exercise in a large proportion of patients, no serious arrhythmia was observed in our study. The probable reason was our exclusion of patients with overt sinoatrial node dysfunction or other types of arrhythmia on the rest electrocardiogram.

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Influence of Stenosis Severity on Coronary Collateral Development and Importance of Collaterals in Maintaining Left Ventricular Function During Acute Coronary Occlusion

STEPHEN E. EPSTEIN, MD

Previous angiographic and histologic studies have demonstrated that human coronary artery collaterals enlarge and mature in response to chronic coronary occlusive disease.[1,2] It also has been shown experimentally and in human subjects that these anatomic changes are associated with substantial enhancement of collateral vessel capacity to deliver blood to the region perfused by the occluded coronary artery[2-9] and that radiographic assessment of the degree of collateral development correlates with the functional capacity of these vessels.[3,4,8,9] Moreover, in the presence of chronic coronary occlusion, coronary collaterals not only enlarge, but also acquire a muscle layer[2,10,11] and become more responsive to the vasodilator effects of nitroglycerin.[12-14]

Rentrop and colleagues[15] have now extended these findings in a series of extremely important observations. First, they demonstrated what has been intuited by clinicians for many years. Namely, that when the site of coronary occlusion is in the right coronary artery or in the mid or distal left anterior descending coronary artery, the occlusion is less likely to precipitate marked left ventricular dysfunction than it would if it occurred in the proximal left anterior descending coronary artery. Second, they found that, for any given location of acute coronary occlusion, the degree of left ventricular function deterioration depends on the presence or absence of collaterals: the more extensive the collaterals, the less deterioration in left ventricular function. Third, they established an inverse quantitative relation between stenosis severity and collateral function.

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Address for reprints: Stephen E. Epstein, MD, Cardiology Branch, 10-7B14, National Heart, Lung, and Blood Institute, Bethesda, Maryland 20892.

The data elucidating the quantitative relation between stenosis severity and extent of collateral development are especially intriguing and of potentially great clinical importance. In the series of patients studied by Rentrop et al, collaterals could not be visualized in patients with a coronary stenosis producing <70% narrowing. Once this threshold stenosis was reached, the magnitude of collateral development—assessed both angiographically and functionally—became greater as stenosis severity increased beyond 70%. The clinical relevance of these anatomic and functional results was substantiated by the course of patients who developed total coronary occlusion as a complication of elective angioplasty. The most severe hemodynamic compromise, including shock and ultimately death, occurred in those patients with proximal left anterior descending coronary stenoses that produced <70% narrowing before angioplasty.

These observations have interesting clinical implications, aside from those relating to coronary angioplasty. They suggest that profound left ventricular dysfunction would more likely develop after an acute spontaneous occlusion of a left anterior descending coronary artery with an underlying lesion causing <70% diameter stenosis, than after an occlusion of a more severely stenotic vessel. Thus, when an acute occlusive event occurs, the patient identified as having "only" a single 50% stenosis involving the proximal left anterior descending coronary artery might, in fact, be at higher risk of developing a hemodynamically severe acute infarction, or of dying, than the individual with a 90% stenosis. This concept undermines, at least in part, our traditional risk stratification approach to coronary artery disease patients, i.e., the common assumption that a patient with a 50% coronary diameter stenosis is at a lower risk than a patient with a narrowing producing 90% diameter narrowing. This is not to say that mild coronary stenoses pose greater net hazards *for an occlusive event occurring* than would

high-grade stenoses. In fact, the risk of an event occurring in a patient with a mild stenosis appears to be considerably less than that of the patient with a stenosis producing a >70% narrowing.[16,17] However, when an acute occlusion does occur in the patient with the mild stenosis, it is likely that the event will precipitate greater hemodynamic and clinical consequences.

These same considerations may relate to the issue of how much time can elapse from the precipitation of acute coronary occlusion before irreversible myocardial damage develops and coronary reperfusion no longer has beneficial effects. On the basis of these considerations, a patient with no ischemic symptoms before the occlusive event most likely will have had an underlying stenosis causing <70% narrowing, and therefore inadequate collaterals. This patient probably will develop myocardial necrosis soon after the precipitation of the acute occlusion, whereas the patient with long-standing angina will more likely than not have a more severe stenosis which, with time, will stimulate collateral growth. Such a patient might benefit from reperfusion long after the acute occlusive event occurred.

The inverse relation between stenosis severity and collateral development probably also partly explains the clinical dilemma as to why sudden death, or an acute infarction causing major destruction of myocardial tissue (often resulting in left ventricular aneurysm formation), occurs so commonly when the acute infarction is the *initial* presenting manifestation of coronary artery disease.[18,19] As above, the lack of any prior symptom suggests a very high likelihood that the underlying stenoses are ≤50%, a finding not uncommonly observed in patients experiencing an acute infarction who undergo early cardiac catheterization and thrombolytic therapy.[20] It would be unlikely for such a patient to have extensive collaterals and, if the acute occlusion were to involve the proximal left anterior descending coronary artery, the patient probably would be at high risk of either dying or of developing a large infarction.

The inverse relation between stenosis severity and collateral development may also explain why the value of exercise screening studies in totally asymptomatic subjects is so problematic. In the Seattle Heart Watch Study,[21] after several thousand asymptomatic middle-aged individuals were screened by exercise stress testing and risk factor analysis, a relatively small percentage of subjects exhibited abnormal test results, while the far larger subgroup had no abnormal findings. As expected, a much greater percentage of patients with abnormal results developed subsequent cardiac events. However, although the patients with normal outcomes experienced a low *percentage* of cardiac events, it was ironic that of the *total number* of events occurring in the entire study population, most derived from the very large "low-risk" subgroup.

Why should sudden deaths occur in the patients with normal stress tests? The results of Rentrop et al, and our more recent understanding of the pathophysiology of acute coronary occlusive syndromes, suggest an answer. It is probable that many middle-aged or older individuals who, despite a normal exercise stress test, have a mild stenosis present in the coronary bed that produces <50% diameter narrowing but does not cause ischemia and consequently, provides no stimulus for collateral development. In addition, coronary atherosclerosis may impair normal endothelial function.[22-24] This may result in the vessel being both more sensitive to stimuli able to cause coronary vasoconstriction, and more likely to stimulate platelet aggregation and fibrin deposition. The atherosclerotic plaque, even though it is not causing a hemodynamically significant stenosis, could also rupture, exposing flowing blood to thrombogenic elements in the vessel wall and thus further facilitate platelet deposition and fibrin formation.[25] Hence, when compared to a perfectly normal vessel, even disease mild enough to produce no clinical evidence of myocardial ischemia probably increases the risk of the eventual precipitation of an occlusive event which, because no collaterals had the opportunity to develop, would then lead to a catastrophic outcome.

These concepts probably apply only to patients with 1-vessel coronary artery disease or patients with multivessel disease with no narrowing >50% in diameter. The reason for this restricted interpretation can be illustrated by the extreme example of the patient with 3-vessel disease and extensive collaterals who has 2 total occlusions and a 90% narrowing of the coronary artery supplying the collaterals. An acute occlusion of this artery would be clinically disastrous, the opposite of what would be expected in the patient with 1-vessel disease and extensive collaterals. The catastrophic outcome, however, would reflect the critical importance of these collaterals. Thus, if their feeder artery were to occlude, collateral blood flow would fall precipitously and result in severe dysfunction of the dependent myocardium with ensuing profound hemodynamic compromise. In the patient with severe narrowing of a single coronary artery, its acute occlusion would not compromise existing coronary collateral flow because it would be the "recipient" rather than "feeder" vessel.

Thus, compelling evidence now indicates that the consequences of an acute coronary occlusion, at least in patients with 1-vessel disease, depend both on the location of the occlusion, which determines the mass of myocardium at risk, and on the severity of the underlying stenosis, which determines the degree of collateralization. Because the latter 2 factors relate *inversely* to each other, there would appear to be an *inverse* relation between stenosis severity and the consequences of an acute coronary occlusive event. These concepts are likely to have important clinical implications relating to risk stratification of patients with coronary artery disease and probably will influence our therapeutic approaches to many such patients.

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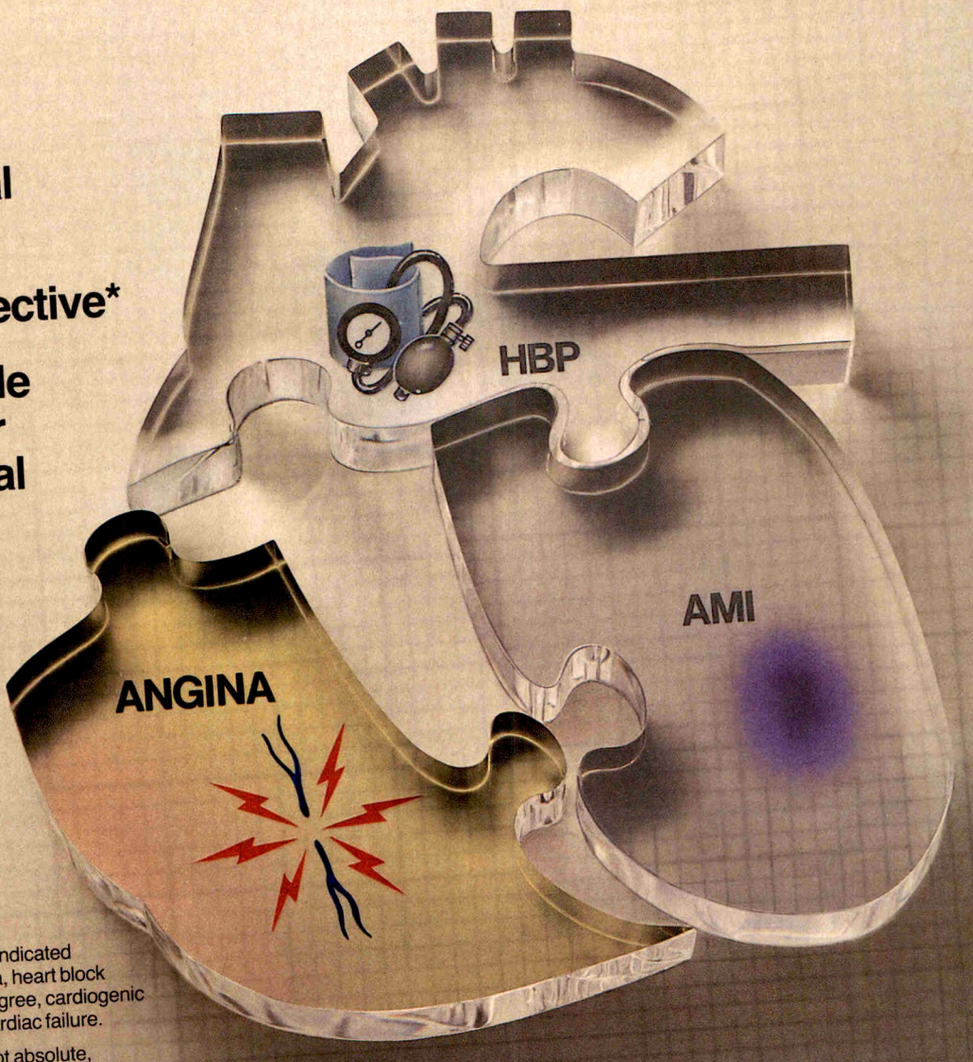

Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

*Exerts a relative, not absolute, preference for beta-one receptors.

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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.
Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS.**)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.
Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.
Treatment
There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

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Left Axis Deviation and Left Anterior Fascicular Block

DAVID H. SPODICK, MD, DSc

Axis is common electrocardiographic shorthand for the mean manifest frontal plane QRS vector, omitting, by convention, not only the P, ST and T axes, but also the horizontal and sagittal plane QRS axes and the spatial QRS vector—the true net axis. Deviation of the frontal plane axis has long been a useful clinical finding,[1] serving even as a screening criterion for cardiac disease.[2] The pioneering contributions of Rosenbaum et al[3] strengthened electrocardiographic axis determination both in concept and in practice, yet cardiologists have perhaps been overenthusiastic in equating marked ($\geq -40°$) and occasionally *any* axis deviation to the left of $-30°$, or even $0°$, with left anterior fascicular ("hemi-") block. Undoubtedly, a marked left axis deviation is nearly always pathologic[2,4] and lesions blocking the anterior radiation of the left bundle system can produce left axis deviation. In addition, because the facile term "left anterior fascicular block" seems weightier than the straightforward and descriptive "left axis deviation," it has tended to displace the latter in electrocardiogram interpretation, even when Rosenbaum's criteria have not been fulfilled.[3] Yet, electrocardiographers should be more critical for at least 2 reasons. First, the left bundle system is not simply bifascicular or even trifascicular, but rather appears to be multifascicular[4–8] (making "fascicular block" more appropriate than "hemiblock"), albeit with strong anterior and posterior fascicular projections. Second, the Einthoven Triangle, a convenient and valuable (but erroneous) approximation from which frontal axes are plotted, necessarily confounds the accuracy of axis determination. Another contributor to some inaccuracy is the use of wave amplitudes rather than areas to calculate axes.

From the Cardiology Division, Saint Vincent Hospital and the Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts. Manuscript received October 26, 1987; revised manuscript received and accepted December 10, 1987.

Address for reprints: David H. Spodick, MD, Division of Cardiology, Saint Vincent Hospital, Worcester, Massachusetts 01604.

Alternative Lesions Producing Left Axis Deviation

Recent histopathologic studies[9] in even marked left axis deviation support previous anatomic demonstrations[4–8,10] of the complexity of the left ventricular conduction system, as well as the intricate distribution of lesions underlying electrocardiographic findings typical of left anterior fascicular block, some of which are located quite proximally.[9] This has been pointed out in the clinical literature along with the probability that left axis deviation can equally be due to myocardial lesions—traditionally, "periinfarction"[11] and "parietal"[12] blocks—in the anterolateral and basal left ventricles.[13] With some such myocardial lesions (admittedly, ill-defined), conduction would be so slowed by the injury or scar that this zone generates the final vector causing the terminal, and often, the net, left ventricular electromotive forces to point toward it, i.e., well to the left in the frontal plane. This does not negate the likelihood of reentry into the fascicular system distal to its interruption by such lesions.

Whereas the effects of the myocardial lesions noted require further investigation, detailed studies of the conduction system in patients by Nakaya et al[9] demonstrated anew that the left ventricular conduction system is "fan-like and spread broadly over the left septal surface." Most lesions associated with left axis deviation, although peripheral, were quite extensive. In others, the lesions were small and confined to the initial (proximal) left ventricular conduction system. This supported the proposal that in the left ventricle's conduction system the "wires" ultimately reaching the anterolateral fascicle must have their origin proximally in the common "cable," i.e., the bundle,[14] so that their selective interruption far from the left anterior fascicle would equally cause left axis deviation. Moreover, the His bundle proper is distinguished by longitudinal orientation of fibers with collagen partitions,[15] predisposing to such "longitudinal dissociation" when those proximal fibers are selectively injured. The point is that the electrocardiogram in such cases of strictly proximal injury is equivalent to that of peripheral (truly fascicular) lesions. Although left axis deviation is associated with left-sided heart disease,[2,4] it is a gross

correlate and some apparently normal subjects also have left axis deviation.[6] Moreover, the detailed anatomic studies of Nakaya et al[9] indicate that the variability in the location of lesions in patients with disease associated with left axis deviation explains why the prognosis is not uniform in them. Any strictly myocardial lesions responsible for left axis deviation would equally contribute to such nonuniformity. Indeed, in the investigations of Nakaya et al, both myocardial and conduction system lesions were present in several patients.[9]

Axis Determination: A Useful Oversimplification

Axis—mean manifest vector—has for long been a useful concept. It is expressed mathematically and, because it yields a number calculated to anywhere from a single degree to 15°, may lend undue confidence in its significance. Moreover, such mathematical expressions depend upon agreed reference systems, in this case the Einthoven Triangle, and over large numbers of subjects, deviation of axis from "normal" does prove useful.[1,2] However, clinicians and investigators frequently encounter exceptions. A principal reason for this, in terms of frontal plane axis, is the fact that the Einthoven reference frame is very helpful, but confounding owing to its gross oversimplification.

The Einthoven Triangle is equilateral. Unfortunately, nothing in nature is equilateral—or perfectly straight, smooth, round, spherical or orthogonal. We use it because it is infinitely simpler to calculate from than, for example, the Burger Triangle,[15] which is a scalene triangle that more accurately represents the imbalances among limb lead electromotive forces. A scalene triangle is not readily applied in practice, whereas the simple equilateral Einthoven Triangle permits us to measure, and even "eyeball," frontal axes with great precision (though with uncertain accuracy in terms of a "true" axis). Indeed, the predictive ability of the "axis" has been sufficient to permit acquisition of a practical data base of clinical and epidemiologic material. Yet, clinicians and investigators must be constantly aware that this useful approximation necessarily errs in individual patients. Finally, omission of the horizontal, sagittal and spatial axes with even more complicated problems of calculation must also contribute to uncertainty.

A situation analogous to Einthoven Triangle use is the application of the La Place relation to express ventricular wall tension. Conceptually, it has been very useful, despite the fact that it applies strictly to a thin-walled, isotropic sphere and the heart is not thin-walled, not isotropic and not a sphere. Increasing physiologic sophistication has replaced it with more realistic left ventricular models (e.g., the prolate ellipsoid of determinate wall thickness) and parameters such as wall stress. Fortunately, comparably increasing sophistication in understanding the complexities of the conduction system has not yet equally reduced the practical utility of axis oversimplification.

Axis Interpretation

While left fascicular lesions may well be the principal cause of left axis deviation, electrocardiogram interpreters cannot know that this is the cause in a given patient because of the alternative mechanisms for left axis deviation. What the electrocardiographer *actually* sees is left axis deviation. Thus, this is all that need be reported. The knowledgeable clinician and investigator will know that 1 explanation of left axis deviation is left anterior fascicular block, but, irrespective of whether it is the most likely explanation—and I believe this to be the case—it is a presumption. The situation is analogous to Q-wave and non-Q-wave myocardial infarcts. For decades, Q-wave infarcts were termed "transmural," i.e., equated with *anatomically* transmural infarction. This is often demonstrably wrong,[16] and, in fact, was inadequately supported in the original literature equating the two.[16] Although most Q-wave infarcts may well be anatomically transmural, all are certainly not, whereas many non-Q-wave infarcts are. Therefore, clinicians, electrocardiographers and investigators now report exactly what they see: a Q-wave infarct. Similarly, left axis deviation should be reported as such because that is what is seen. The knowledgeable manager of such information will know that transmurality and fascicular block, respectively, are highly likely, but not exclusive explanations.

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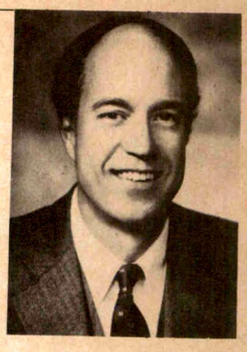

The Logic of Using Either Two Mechanical Valves or Two Bioprosthetic Valves for Replacement of Both Mitral and Aortic Valves

N.G., a 53-year-old woman, at age 26 had mitral commissurotomy for mitral stenosis and at age 41 the stenotic mitral valve was replaced with a bioprosthesis (Hancock) and the regurgitant aortic valve, with a Bjork-Shiley prosthesis. At age 52, the bioprosthesis in the mitral position had degenerated (severely regurgitant) and it was now replaced with a St. Jude medical prosthesis. Multiple complications occurred postoperatively and she died in February 1988, 40 days after the third cardiac operation. Had the mitral valve been replaced 11 years earlier with a prosthetic rather than a bioprosthetic valve, it is unlikely that a third operation would have been required. After the second operation, she received daily warfarin therapy because of the prosthetic valve in the aortic valve position.

This case is not an infrequent occurrence. Among 54 patients having simultaneous replacement of both mitral and aortic valves and studied later at necropsy by Roberts and Sullivan,[1] 38 (70%) had mechanical prostheses in both valve positions, 4 (8%) had bioprostheses in both valve positions and 12 (22%) had 1 mechanical prosthesis and 1 bioprosthesis. To utilize a bioprosthesis in 1 left-sided valve position and a mechanical prosthesis in the other left-sided valve position is illogical because the advantages of each type of substitute valve are lost by the presence of the other type of substitute valve. The advantage, of course, of a mechanical prosthesis is that it should not wear out; its disadvantage is that all patients having one need long-term anticoagulant (warfarin) therapy. In contrast, the advantage of the bioprosthesis is that patients having one do not need long-term anticoagulant therapy; the disadvantage of the biopostheses is that it wears out if the patient lives long enough, usually 5 to 15 years, and then another operation is required. Thus, the placing of 1 bioprosthetic valve and 1 mechanical valve in the same patient translates into the loss for the patient of each of the advantages of the mechanical and bioprosthetic valves, and at the same time, the gain for the patient of the disadvantages of each of the 2 types of substitute cardiac valves. Either both left-sided valve substitutes should be mechanical prostheses or both should be bioprostheses!

William C. Roberts

William C. Roberts, MD
Editor in Chief

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LETTERS*

CORRECTION AND CLARIFICATION ON TYPE OF 24-HOUR ELECTROCARDIOGRAPHIC ANALYZERS FOR VENTRICULAR ARRHYTHMIA DESCRIBED IN A RECENT PUBLICATION

Our article published in the December 1987 issue of the *AJC* contains the following error.[1] The CardioData Mark II analyzer was used for analysis of the recordings in that article, whereas the article erroneously reported that the Mark III analyzer was used. The Mark II analyzer preceded the Mark III in time and contained earlier versions of analysis software. This difference may have important implications on the applicability of the findings to today's scanning devices.

Three points are also worth making for purposes of clarification. First, for the interpretation of the data obtained on any device, it may be important to know the dates within which the analyes were made, as software updates may alter the accuracy of the analysis algorithms. The recordings were analyzed on the CardioData device between February 25, 1981, and October 15, 1981. The recordings were analyzed on the Avionics device between August 25, 1981, and August 26, 1982. Subsequent software upgrades may have altered the performance of the devices for quantitation of ventricular premature complexes.

Second, our report demonstrated that both the devices we tested had difficulty quantifying nonsustained ventricular tachycardia. Although, for research purposes, quantitation of nonsustained ventricular tachycardia is important, this quantitation may not be critical for clinical purposes. In fact, the detection of any events of nonsustained ventricular tachycardia before therapy and confirmation of "complete elimination" of these events on therapy may be a reasonable goal for devices used for clinical purposes. There were 6 recordings in our study that contained events of nonsustained ventricular tachycardia. The scanners successfully detected at least some of these events on each recording. Conversely, the final analysis report did not describe nonsustained ventricular tachycardia in any of the recordings that did not have such events detected by hand counting. Thus, these 2 devices appear reliable for the qualitative detection of nonsustained ventricular tachycardia, and therefore should be adequate for clinical purposes.

Finally, we tested the accuracy of the device and technician as a single unit. In all cases, the technician was allowed to interact with the analyzer and edit the data from the scanner. Technician decision errors in the identification of beats may have contibuted to the errors that we detected in the device-technician unit. However, since these devices are designed to function optimally with technician interaction, we felt it was inappropriate to test the equipment without this interaction.

David M. Salerno, MD, PhD
Gregory Granrud, MD
Morrison Hodges, MD
Minneapolis, Minnesota
5 February 1988

1. Salerno DM, Granrud G, Hodges M. *Accuracy of commercial 24-hour electrocardiogram analyzers for quantitation of total and repetitive ventricular arrhythmias. Am J Cardiol 1987;60:1299-1305.*

CORRECTION

A fairly gross error was made in the publication of our article entitled "Linking by Collision Initiated in the Absence of Preexisting Reentrant Tachycardia: Electrophysiologic Demonstration and Significance," which appeared in the February 1988 *Journal*, pages 254 to 260.

The error involved transposition of the entire second paragraph from the legend of Figure 3 to the legend of Figure 2. Although all errors are unfortunate, this one in particular "hurts" because Figure 3 is so complex and plays a pivotal role in the concepts we endeavored to advance in our article.

Michael H. Lehmann, MD
Detroit, Michigan
12 February 1988

CORRECTION

It has come to my attention that there is an error in Table II of our article, "Echo Doppler Assessment of Cardiac Output and Its Relation to Growth in Normal Infants," published in the November 1987 *Journal*, pages 1112 to 1116.

The regression equations for cardiac output and stroke volume against weight given in the second line are incorrect. The regression equation for cardiac output should read $1.11 \times W + 0.19$, and the regression equation for stroke volume should read $1.0 \times W + 0.6$.

Gary F. Sholler, MB, BS, FRACP
for the authors
Sydney, Australia
25 January 1988

SURGICAL AND MEDICAL RESULTS OF COMPLETE ATRIOVENTRICULAR CANAL

I was surprised that Clapp et al[1] did not state the number of patients with the Down syndrome in their article. Although it was not the intent of their review to compare patients with Down syndrome and nonsyndromic patients, this important variable should have been included in at least part of their analysis. Complete atrioventricular canal is the most common cardiac defect in this syndrome; of patients with complete atrioventricular canal most have the Down syndrome. The postulated propensity toward pulmonary vascular obstructive disease in Down syndrome and its possible effect on morbidity and mortality should have been addressed. The presence of a chromosomal malformation syndrome in a patient with a congenital cardiac defect is not trivial.

Angela E. Lin, MD
Pittsburgh, Pennsylvania
5 March 1987

1. Clapp SK, Perry BL, Farooki ZQ, Jackson WL, Karpawich PP, Hakimi M, Arciniegas E, Green E. *Surgical and medical results of complete atrioventricular canal: a ten year review. Am J Cardiol 1987;59:454-458.*

AGING, MYOCARDIAL COMPLIANCE AND VENTRICULAR FILLING SOUNDS

Bryg and colleagues[1] have contributed significantly to the understanding of aging effects on left ventricular diastolic filling in normal subjects, which may be related to the well-known decrease in compliance of the left ventricle with normal aging. This same phenomenon has been seen in the typical low-compliance of abnormal hearts in coronary artery disease, dilated cardiomyopathy and hypertrophic cardiomyopathy[2] (in the absence of mitral regurgitation as also shown by Bryg and associates[3]). These differences agree nicely with the demonstration by Shaver and colleagues[4] of the mechanism of the normal third heart sound and with our studies showing an increased prevalence and audibility of fourth heart sounds with aging in normal subjects. Although it is not a part of their investigation, would the authors have any information on the prevalence of third and fourth heart sounds in their population?

David H. Spodick, MD, DSc
Worcester, Massachusetts
5 May 1987

1. Bryg RJ, Williams GA, Labovitz AJ. *Effect of aging on left ventricular diastolic filling in normal subjects. Am J Cardiol 1987;59:971-974.*
2. Toeda T, Hoshino Y, Yamazoe, Arai Y. *Factors influencing the atrial contribution to ventricular filling. Jpn Circulation J 1986;50:772-773.*
3. Bryg RJ, Pearson DC, Williams GA, Labovitz AJ. *Left ventricular systolic and diastolic flow abnormalities by Doppler in obstructive cardiomyopathy. Am J Cardiol 1987;59:925-931.*
4. Shaver JA, Keddy DS, Alvares RF, Saleni R. *Genesis of the physiologic third heart sound. Am J Noninvasive Cardiol 1987;1:39-55.*

REPLY: Several recent studies using Doppler echocardiography as well as phonocardiog-

* Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

raphy have demonstrated the increasing importance of atrial contribution to ventricular filling with aging. This phenomenon is believed to reflect alterations in left ventricular filling as the chamber becomes less compliant and is represented in the Doppler tracing as an increase in the atrial filling velocity when compared with the early diastolic filling velocities and, on phonocardiography or auscultation, by an increased prominence of the fourth heart sound. The etiology of the third heart sound, however, remains more enigmatic. A careful record of the prevalence of third and fourth heart sounds unfortunately was not recorded in our recently published study. We suspect, however, as Dr. Spodick suggests, that the fourth heart sound would have been heard more frequently in the older subjects and would have correlated inversely with the early diastolic to atrial velocity ratio. We have had the opportunity to recently evaluate 150 elderly individuals (mean age 70) with signs and symptoms suggestive of congestive heart failure. Of note was the fact that two thirds of these patients (group 1) had decreased left ventricular ejection fraction, while one third of them (group 2) had normal left ventricular ejection fractions and implied symptoms of heart failure secondary to abnormal diastolic function. While there was no significant difference in the prevalence of the fourth heart sound in these 2 groups (43 vs 42%), the third heart sound was significantly more prevalent in patients with abnormal systolic function (42 vs 21%, $p < 0.05$). These findings suggest that the genesis of the third heart sound is probably not a simple reflection of left ventricular chamber compliance. Further studies in normal elderly individuals comparing Doppler and phonocardiographic findings would be of great interest.

Arthur J. Labovitz, MD
St. Louis, Missouri
26 May 1987

SIGNIFICANCE OF HIGH CK-MB/CK RATIOS WITH NORMAL CREATINE KINASE IN ACUTE MYOCARDIAL INFARCTION

Yusuf et al[1] reported on the significance of elevated creatine kinase (CK)-MB isoenzyme with normal CK values. They related the occurrence of this phenomenon to the existence of small myocardial infarctions. Since the introduction of CK-MB as a diagnostic parameter in clinical chemistry,[2] a lot of atypical CK isoenzyme patterns and atypical CK forms have been described.[3] As the heart tissue isoenzyme distribution of CK is altered by hypoxia,[4] the diagnostic specificity of CK-MB has recently been rediscussed. As hypoxic tissues preferably synthesize CK-B subunits, relative elevated CK-MB levels associated with normal CK activities have to be interpreted with care in patients with ischemic heart disease.

Spincemaille et al[5] demonstrated false-positive results of CK-MB analysis when ion-exchange techniques were used. Both macro CK-I and subisoenzymes of CK-MM have been shown to interfere with ion-exchange techniques. Further, in coronary artery disease, macro CK-I is a common finding. Up to 13% of patients with angiographically proven coronary artery disease were reported to be positive on macro CK-I.[6]

Physiochemical properties of CK-MB are not so significantly different from those of the other CK forms (M_r 85,000), simultaneous release of both CK-isoenzymes (CK-MM and CK-MB) can be expected. As the biological half-life of CK-MB is even shorter than that of CK-MM, one would expect that infrequent sampling can merely lead to false-negative CK-MB results. Prolonged "CK-MB" activity is most likely due to the presence of macro-CK, which is characterized by a long biological half-life time. The apparently long CK-MB half-life as reported in the article can be explained by the presence of macro-CK.

In the 4 diagnostic groups, as described by Yusuf et al[1], most atypical CK patterns are observed in group 2 (patients with history of angina and acute myocardial infarction). In these 2 conditions, the prevalence of macro CK-I has been reported to be high.

As Yusuf et al demonstrated the difficulties in interpreting CK/CK-MB analysis in patients with established cardiac disease, one should recommend highly specific methods for measuring CK-MB concentrations, such as electrophoresis or immuno-precipitation, which are less sensitive to aberrant CK forms.[7]

Joris Delanghe, MD
Marc De Buyzere, BSc
Ivan De Scheerder, MD
Ghent, Belgium
7 May 1987

1. Yusuf S, Collins R, Lin L, Sterry H, Pearson M, Sleight P. *Significance of elevated MB isoenzyme with normal creatine kinase in acute myocardial infarction. Am J Cardiol 1987;59:245–250.*
2. Mercer DW, Varat MA. *Detection of cardiac specific creatine kinase in sera with normal or slightly increased total creatine kinase activity. Clin Chem 1975;21:1088–1097.*
3. Lang H, Wurzburg U. *Creatine kinase, an enzyme of many forms. Clin Chem 1982;28:1439–1447.*
4. Ingwall J, Kramer M, Fifer M, Lorell B, Shemin R, Grossman W, Allen P. *The creatine kinase system in normal and diseased myocardium. N Engl J Med 1986;313:1050–1054.*
5. Spincemaille J, Delanghe J, De Buyzere M, Breemeersch M, Blaton V. *Evaluation of three current methods for the determination of creatine kinase-MB catalytic activity. J Clin Chem Clin Biochem 1984;22:603–607.*
6. Delanghe J, De Scheerder I, De Buyzere M, Algoed L, Robbrecht J. *Macro CK type I as a marker for auto-immunity in coronary heart disease. Atherosclerosis 1986;60:215–219.*
7. McBride JH, Rodgerson DO, Diamond LJ. *Creatine kinase isoenzyme MB as measured by anion-exchange chromatography, immunoradiometric assay, and immunometric assay. Clin Chem 1985; 31:1099–1100.*

SILENT ISCHEMIA: AN UNPROVEN THERAPEUTIC CONCEPT

In the April 1, 1987, issue of *The American Journal of Cardiology*, 5 original articles and 2 editorials appeared relating to the extremely popular subject of silent myocardial ischemia. In their editorial, Pepine and associates[1] point out that silent ischemia as detected by stress testing and ambulatory electrocardiographic monitoring is common. They cite rather limited evidence that silent ischemia has important prognostic implications. They next take the giant step of recommending that silent ischemia must be documented and managed.

It is appropriate to investigate this concept thoroughly, but to recommend that clinicians embark on detecting and treating silent ischemia is premature at best and irresponsible at worst. The financial implication of the numerous ambulatory electrocardiogram stress tests, physician visits, drugs, angioplasties and coronary bypass procedures required to stamp out "the total ischemic burden" is staggering to contemplate. In addition, a great number of patients are likely to suffer real harm from well-intentioned treatment. Unfortunately the situation is somewhat analogous to the aggressive, expensive, unproven, often harmful drug therapy of ventricular premature complexes that has been so common in the past 2 decades.

I hope that practicing physicians will show restraint before they submit their patients to unnecessary, expensive tests and treatments in an effort to keep up with the latest popular concept.

Lewis H. Seager, MD
Woodland Hills, California
12 May 1987

1. Pepine CJ, Imperi GA, Hill JA. *Therapeutic implications of silent myocardial ischemia during daily activity. Am J Cardiol 1987;59:993–995.*

REPLY: We appreciate Dr. Seager's interest in our editorial on the implication of silent ischemia and the opportunity to respond. We stated several times that more data are needed but we are concerned that evidence linking silent ischemia and prognosis is becoming very strong. In the interim, it is our best opinion that certain high risk groups should be identified and antiischemic treatment instituted.

Dr. Seager makes a comparison between therapy of ventricular premature complexes and silent ischemia. We caution readers not to equate these 2 entities as Dr. Seager has done. Transient myocardial ischemia, be it silent or painful, is a serious pathologic process which is always associated with left ventricular dysfunction. Active ischemia, either painful or silent, does not occur in the normal heart and there is no question that myocardial ischemia precedes events like myocardial infarction. The antiischemic therapy that we have available (nitrates, calcium antagonists and β blockers) is safe and effective.

Ventricular premature complexes, in contrast, often occur in the setting of a normal heart or nearly normal ventricular function. They are not clearly linked to more malignant arrhythmias in many settings. Ample experience indicates that in many cases, antiarrhythmic therapy is not safe and proarrhythmic effects are a real problem. Efficiency and safety in patients at highest risk (e.g., poor left ventricular function) is not proven.

Finally, Dr. Seager urges restraint relative to the possibility of extensive costs. We must point out that in any cost assessment, one must consider both sides of the cost/benefit equation. If potential benefits (e.g. saving lives and preventing acute myocardial infarctions in relatively healthy productive middle-aged

men with coronary artery disease) appear to outweigh the anticipated costs of treating asymptomatic ischemia, then one can justify our recommendation until additional data are at hand.

Carl J. Pepine, MD
James A. Hill, MD
Gainesville, Florida
29 May 1987

NIFEDIPINE-INDUCED PAROTITIS: A HYPERSENSITIVITY REACTION

Nifedipine has been observed by various indexes to induce adverse effects, such as headache, flushing, dizziness, peripheral edema, weakness and transient hypotension, after oral administration.[1] Other rare pathologic events related to this drug, such as congestive heart failure, myocardial infarction and cerebral ischemia, have been reported.[2] Recently Bosch et al[3] described the first case of nifedipine-related parotitis. We recently studied a patient who developed acute swelling of parotid and salivary glands, after sublingual administration of nifedipine.

A 50-year-old man was admitted for hypertension crisis (220/120 mm Hg of blood arterial pressure) and suspected acute myocardial infarction. The patient was heparynized and treated with buprenorfine, isosorbide, lydocaine and nifedipine (20 mg sublingually every 6 hours). Ten hours later bilateral progressive enlargement of parotid and salivary glands appeared, with painless dry mouth, rhinorrea, fever and skin rash. Laboratory data disclosed virus infection of the parotid gland and nifedipine was interrupted. Three days after steroid therapy all symptoms disappeared and nifedipine was substituted with diltiazem.

Our data suggest a hypersensitivity reaction to nifedipine causing a parotid swelling as it is reported for other drugs.[4,5]

Catarini Massimo, MD
G. Sebastianelli, MD
G. Noera, MD
Cingoli, Italy
12 May 1987

1. American Hospital Formulary Service, Drug Information. *Bethesda: American Society of Hospital Pharmacists, 1986.*
2. Leverson JL, Kennedy K, Dysosmia K. *Disgeusia and nifedipine. Ann Intern Med 1985;102:135–136.*
3. Bosch X, Campistol JM, Botey A, Cases A, Revert LL. *Nifedipine-induced parotitis. Lancet 1986;467.*
4. Mardh PA, Belfrage I, Naversten E. *Sialodenitis following treatment with alfa-metildopa. Acta Med Scand 1974;195:133–135.*
5. Chen JH, Ottolenghi P, Distenfeld A. *Oxyphenbutazone-induced sialodenitis. JAMA 1977;238:1399.*

ART IN CARDIOLOGY

Most illustrations in published articles on cardiology lack artistic originality. We thought your readers might appreciate the artistic value of this untouched illustration of a print-out page from a 24-hour ambulatory electrocardiographic monitoring recording (Figure 1).

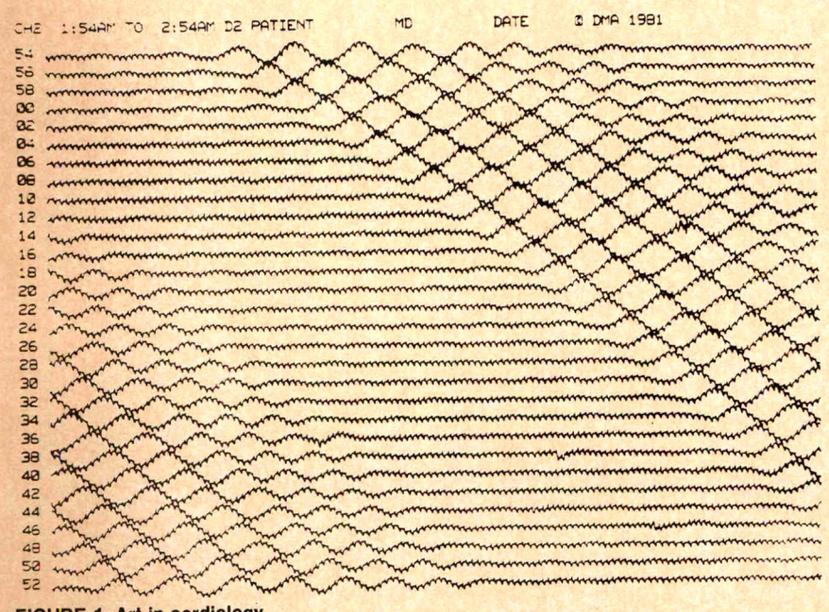


FIGURE 1. Art in cardiology.

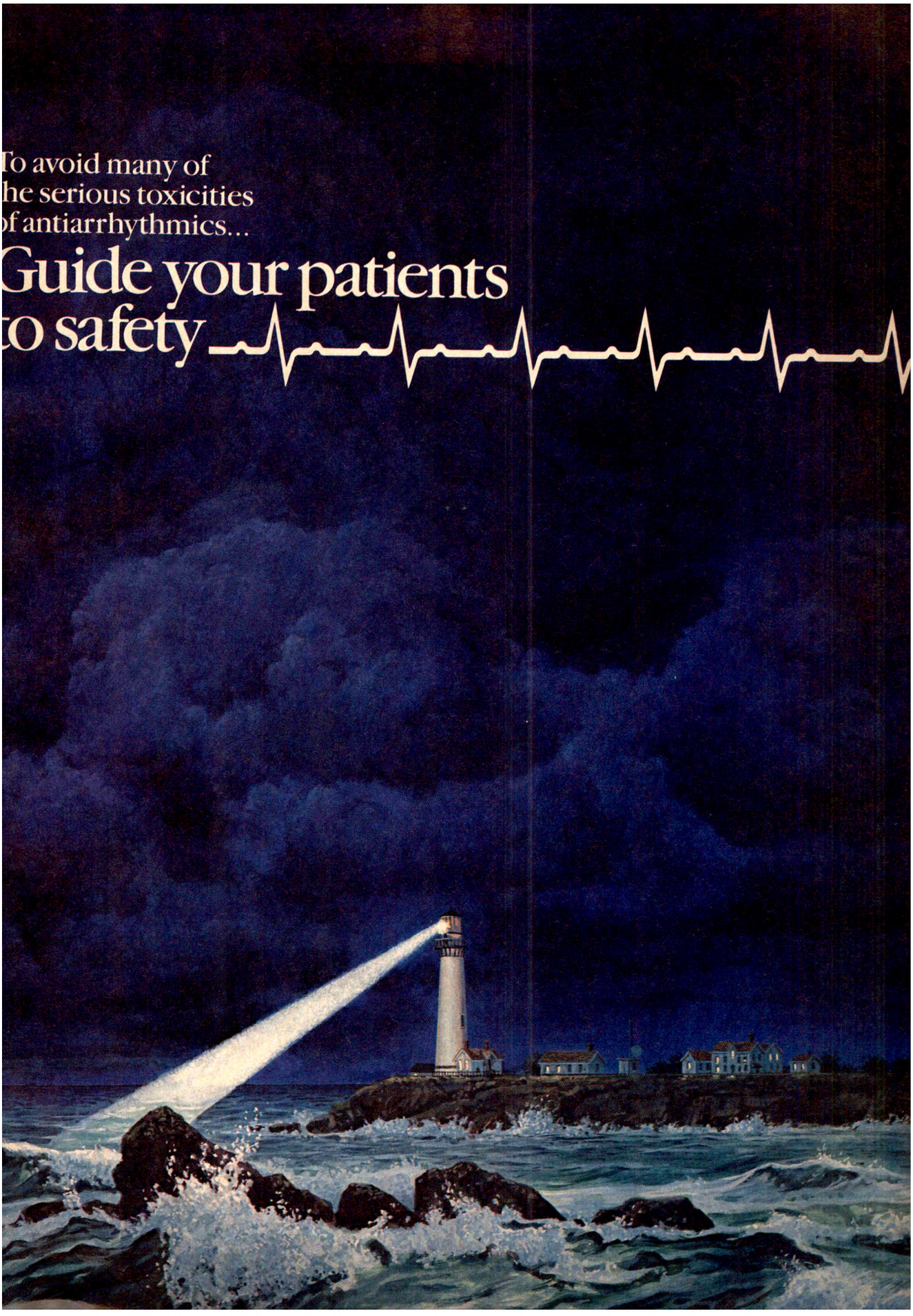
Monty M. Zion
Jonathan Balkin
Rachel Levy
Jerusalem, Israel
11 May 1987

DOPPLER EVALUATION OF DIASTOLIC FLOW IN OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

We read with interest the article by Bryg et al,[1] comparing Doppler parameters of patients with obstructive hypertrophic cardiomyopathy (HC) to normal subjects. We agree that left ventricular (LV) Doppler filling patterns may be altered in patients with HC, and age should be taken into consideration for valid interpretation of the data.[2,3] However, we disagree with the way the data were analyzed. In our opinion, it is inadequate to compare mean values of normal subjects with a wide age range to the mean values of patients with even wider age range. It would have been more appropriate to compare the data from subgroups with narrow age ranges. Alternatively, plotting the data of patients with HC on scattergrams against age of normal subjects (which the authors have previously done),[3] would have presented the results more convincingly. Furthermore, looking at the authors' data, one can appreciate the significant effect of age on LV diastolic filling in patients with HC. Thus, in many of their patients age had a more significant effect on E/A mitral peak velocity ratio than the presence or absence of mitral regurgitation. Age had even more effect on LV filling than the disease itself. Thus, in 4 young subjects with HC without mitral regurgitation the E/A ratio was high. In patient 11, the E/A was 1.3, while in patients 3, 4 and 12 the ratio was 1.6. Because of the method of analysis of the data the reader might overlook the significance of age on LV filling in patients with HC.

Edward G. Abinader, FRCPI
Dawod S. Sharif, MD
Haifa, Israel
4 September 1987

1. Bryg RJ, Pearson AC, Williams GA, Labovitz AJ. *Left ventricular systolic and diastolic flow abnormalities determined by Doppler echocardiography in obstructive hypertrophic cardiomyopathy. Am J Cardiol 1987;59:925–931.*
2. Kuo LC, Quinones MA, Rokey R, Sartori M, Abinader EG, Zoghbi WA. *Quantitation of atrial contribution to left ventricular filling by pulsed Doppler echocardiography and the effect of age in normal and diseased hearts. Am J Cardiol 1987;59:1174–1178.*
3. Bryg RJ, Williams GA, Labovitz AJ. *Effect of age on left ventricular diastolic filling in normal subjects. Am J Cardiol 1987;59:971–974.*


To avoid many of
he serious toxicities
f antiarrhythmics...
Guide your patients
o safety

Guide them to MEXITIL® (MEXILETINE HCl)

The uncompromising efficacy of a first-line agent

MEXITIL is as effective as quinidine, procainamide, disopyramide, and tocainide in controlling ventricular arrhythmias including PVCs, couplets, and V Tach.[1-6]

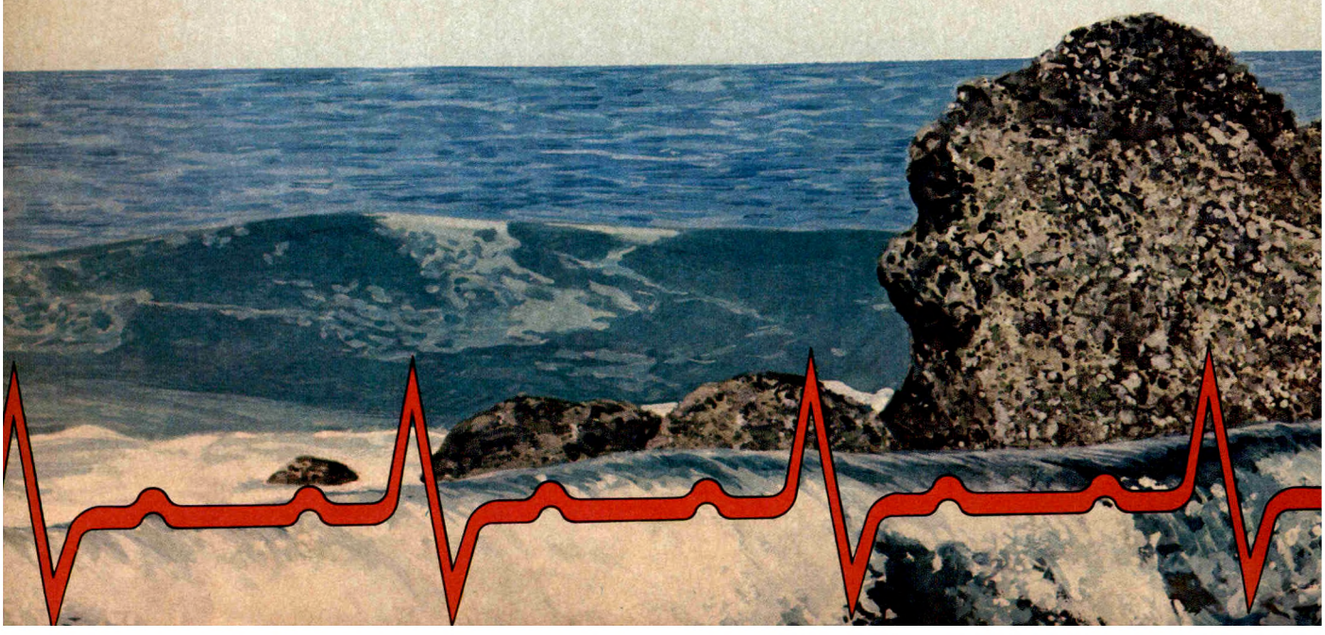
Avoids many late-onset toxicities encountered with other antiarrhythmics

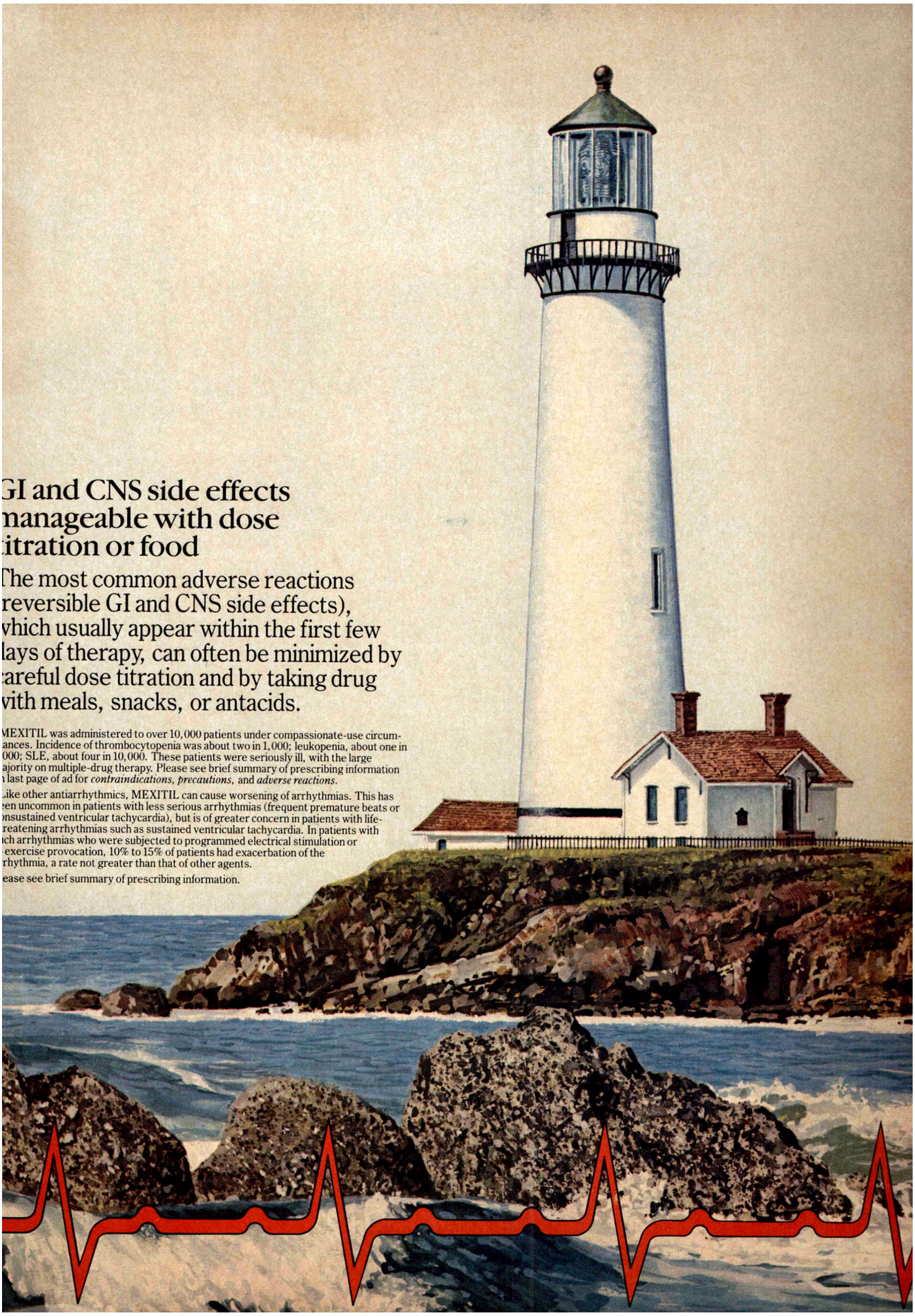
In controlled clinical trials, MEXITIL has not been associated with serious, late-onset toxicities such as hematologic effects, SLE, or pulmonary fibrosis.*

A favorable electrophysiologic and hemodynamic profile

MEXITIL is unlikely to aggravate arrhythmias in the clinical setting.[7-9†] It does not prolong the QT interval and, thus, is less likely than many other antiarrhythmics to produce torsades de pointes.[10,11]

MEXITIL has no significant negative inotropic effect, making it an excellent choice for use in patients with compromised cardiac function.[12-15]





GI and CNS side effects manageable with dose titration or food

The most common adverse reactions (reversible GI and CNS side effects), which usually appear within the first few days of therapy, can often be minimized by careful dose titration and by taking drug with meals, snacks, or antacids.

MEXITIL was administered to over 10,000 patients under compassionate-use circumstances. Incidence of thrombocytopenia was about two in 1,000; leukopenia, about one in 1,000; SLE, about four in 10,000. These patients were seriously ill, with the large majority on multiple-drug therapy. Please see brief summary of prescribing information on last page of ad for *contraindications, precautions,* and *adverse reactions.*

Like other antiarrhythmics, MEXITIL can cause worsening of arrhythmias. This has been uncommon in patients with less serious arrhythmias (frequent premature beats or nonsustained ventricular tachycardia), but is of greater concern in patients with life-threatening arrhythmias such as sustained ventricular tachycardia. In patients with such arrhythmias who were subjected to programmed electrical stimulation or exercise provocation, 10% to 15% of patients had exacerbation of the arrhythmia, a rate not greater than that of other agents.

Please see brief summary of prescribing information.

MEXITIL®
(MEXILETINE HCl)

Distinguished by Its Safety Profile

References: 1. Data on file. Boehringer Ingelheim Pharmaceuticals, Inc. 2. Trimarco B, et al: *Curr Ther Res* 1983;33(3):472–487. 3. Singh JB, et al: *Am J Cardiol* 1984;53:84–87. 4. Fenster PE, Hanson CD: *Clin Pharmacol Ther* 1983;34(2):136–142. 5. Hession M, et al: *J Am Coll Cardiol* 1986;7(2):338–343. 6. Thompson KA, et al: *Clin Res* 1985;33(2):289A. 7. Velebit V, et al: *Circulation* 1982;65(5):886–894. 8. Podrid PJ, et al: *Am J Cardiol* 1987;59:38E–44E. 9. Campbell RWF: *Am J Cardiol* 1987;59:49E–51E. 10. Zipes DP: *Am J Cardiol* 1987;59:26E–31E. 11. Stratmann HG, Kennedy HL: *Am Heart J* 1987;113:1470–1482. 12. Sami M, Lisbona R: *Can J Cardiol* 1985;1(4):251–258. 13. Stein J, Podrid P, Lown B: *Am J Cardiol* 1984;54:575–578. 14. Shanks RG: *Am Heart J* 1984;107:1065–1071. 15. Chadda KD, Weiss P, Bodenheimer MM: *Circulation* 1987;76(suppl 4):IV–179, abstract 0712.

Mexitil®
(mexiletine hydrochloride)
Oral Antiarrhythmic

Capsules of 150 mg, 200 mg and 250 mg

Brief Summary of Prescribing Information

CONTRAINDICATIONS: Mexitil® (mexiletine hydrochloride) is contraindicated in the presence of cardiogenic shock or pre-existing second- or third-degree AV block (if no pacemaker is present).

PRECAUTIONS: General: If a ventricular pacemaker is operative, patients with second or third degree heart block may be treated with Mexitil® (mexiletine hydrochloride) if continuously monitored. A limited number of patients (45 of 475 in controlled clinical trials) with pre-existing first degree AV block were treated with Mexitil; none of these patients developed second or third degree AV block. Caution should be exercised when it is used in such patients or in patients with pre-existing sinus node dysfunction or intraventricular conduction abnormalities.

Like other antiarrhythmics Mexitil can cause worsening of arrhythmias. This has been uncommon in patients with less serious arrhythmias (frequent premature beats or non-sustained ventricular tachycardia: see ADVERSE REACTIONS), but is of greater concern in patients with life-threatening arrhythmias such as sustained ventricular tachycardia. In patients with such arrhythmias subjected to programmed electrical stimulation or to exercise provocation, 10-15% of patients had exacerbation of the arrhythmia, a rate not greater than that of other agents.

Mexitil should be used with caution in patients with hypotension and severe congestive heart failure.

Since Mexitil is metabolized in the liver, and hepatic impairment has been reported to prolong the elimination half-life of Mexitil, patients with liver disease should be followed carefully while receiving Mexitil. The same caution should be observed in patients with hepatic dysfunction secondary to congestive heart failure.

Concurrent drug therapy or dietary regimens which may markedly alter urinary pH should be avoided during Mexitil therapy. The minor fluctuations in urinary pH associated with normal diet do not affect the excretion of Mexitil.

SGOT Elevation and Liver Injury: In three-month controlled trials, elevations of SGOT greater than three times the upper limit of normal occurred in about 1% of both mexiletine-treated and control patients. Approximately 2% of patients in the mexiletine compassionate use program had elevations of SGOT greater than or equal to three times the upper limit of normal. These elevations frequently occurred in association with identifiable clinical events and therapeutic measures such as congestive heart failure, acute myocardial infarction, blood transfusions and other medications. These elevations were often asymptomatic and transient, usually not associated with elevated bilirubin levels and usually did not require discontinuation of therapy. Marked elevations of SGOT (>1000 U/L) were seen before death in four patients with end-stage cardiac disease (severe congestive heart failure, cardiogenic shock).

In foreign marketing experience rare instances of severe liver injury, including hepatic necrosis, have been reported in association with Mexitil treatment. It is recommended that patients in whom an abnormal liver test has occurred, or who have signs or symptoms suggesting liver dysfunction, be carefully evaluated. If persistent or worsening elevation of hepatic enzymes is detected, consideration should be given to discontinuing therapy.

Blood Dyscrasias: Blood dyscrasias were not seen in the controlled trials. Among 10,867 patients treated with mexiletine in the compassionate use program, marked leukopenia (neutrophils less than 1000/mm^3) or agranulocytosis were seen in 0.06%, and milder depressions of leukocytes were seen in 0.08%, and thrombocytopenia was observed in 0.16%. Many of these patients were seriously ill and receiving concomitant medications with known hematologic adverse effects. Rechallenge with mexiletine in several cases was negative. Marked leukopenia or agranulocytosis did not occur in any patient receiving Mexitil alone; five of the six cases of agranulocytosis were associated with procainamide (sustained release preparations in four) and one with vinblastine. If significant hematologic changes are observed, the patient should be carefully evaluated, and, if warranted, Mexitil should be discontinued. Blood counts usually return to normal within one month of discontinuation. (See ADVERSE REACTIONS.)

Convulsions (seizures) did not occur in Mexitil controlled clinical trials. In the compassionate use program, convulsions were reported in about 2 of 1000 patients. Twenty-eight percent of these patients discontinued therapy. Convulsions were reported in patients with and without a prior history of seizures. Mexiletine should be used with caution in patients with known seizure disorder.

Drug Interactions: In a large compassionate use program Mexitil has been used concurrently with commonly employed antianginal, antihypertensive, and anticoagulant drugs without observed interactions. A variety of antiarrhythmics such as quinidine or propranolol were also added, sometimes with improved control of ventricular ectopy. When phenytoin or other hepatic enzyme inducers such as rifampin and phenobarbital have been taken concurrently with Mexitil, lowered Mexitil plasma levels have been reported. Monitoring of Mexitil plasma levels is recommended during such concurrent use to avoid ineffective therapy.

In a formal study, benzodiazepines were shown not to affect Mexitil plasma concentrations. ECG intervals (PR, QRS and QT) were not affected by concurrent Mexitil and digoxin, diuretics, or propranolol.

Concurrent administration of cimetidine and Mexitil has been reported to increase, decrease, or leave unchanged Mexitil plasma levels; therefore patients should be followed carefully during concurrent therapy.

Mexitil does not alter serum digoxin levels, but magnesium-aluminum hydroxide, when used to treat gastrointestinal symptoms due to Mexitil, has been reported to lower serum digoxin levels.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Studies of carcinogenesis in rats (24 months) and mice (18 months) did not demonstrate any tumorigenic potential. Mexitil was found to be non-mutagenic in the Ames test. Mexitil did not impair fertility in the rat.

Pregnancy/Teratogenic Effects

Pregnancy Category C: Reproduction studies performed with Mexitil in rats, mice and rabbits at doses up to four times the maximum human oral dose (20 mg/kg in a 50 kg patient) revealed no evidence of teratogenicity or impaired fertility but did show an increase in fetal resorption. There are no adequate and well-controlled studies in pregnant women; this drug should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Mexitil appears in human milk in concentrations similar to those observed in plasma. Therefore, if the use of Mexitil is deemed essential, an alternative method of infant feeding should be considered.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Mexitil® (mexiletine hydrochloride) commonly produces reversible gastrointestinal and nervous system adverse reactions but is otherwise well tolerated. Mexitil has been evaluated in 483 patients in one-month and three-month controlled studies and in over 10,000 patients in a large compassionate use program. Dosages in the controlled studies ranged from 600-1200 mg/day; some patients (8%) in the compassionate use program were treated with higher daily doses (1600-3200 mg/day). In the three-month controlled trials comparing Mexitil to quinidine, procainamide and disopyramide, the most frequent adverse reactions were upper gastrointestinal distress (41%), lightheadedness (10.5%), tremor (12.6%) and coordination difficulties (10.2%). Similar frequency and incidence were observed in the one-month placebo-controlled trial. Although these reactions were generally not serious, and were dose-related and reversible with a reduction in dosage, by taking the drug with food or antacid or by therapy discontinuation, they led to therapy discontinuation in 40% of patients in the controlled trials. A tabulation of the adverse events reported in the one-month placebo-controlled trial follows:

Comparative Incidence (%) of Adverse Events among Patients Treated with Mexiletine and Placebo in the 4-Week, Double-Blind Crossover Trial

	Mexiletine N = 53	Placebo N = 49
Cardiovascular		
Palpitations	7.5	10.2
Chest Pain	7.5	4.1
Increased Ventricular Arrhythmias/PVC's	1.9	—
Digestive		
Nausea/Vomiting/Heartburn	39.6	6.1
Central Nervous System		
Dizziness/Lightheadedness	26.4	14.3
Tremor	13.2	—
Nervousness	11.3	6.1
Coordination Difficulties	9.4	—
Changes in Sleep Habits	7.5	16.3
Paresthesias/Numbness	3.8	2.0
Weakness	1.9	4.1
Fatigue	1.9	2.0
Tinnitus	1.9	4.1
Confusion/Clouded Sensorium	1.9	2.0
Other		
Headache	7.5	6.1
Blurred Vision/Visual Disturbances	7.5	2.0
Dyspnea/Respiratory	5.7	10.2
Rash	3.8	2.0
Non-specific Edema	3.8	—

A tabulation of adverse reactions occurring in one percent or more of patients in the three-month controlled studies follows:

Comparative Incidence (%) of Adverse Events among Patients Treated with Mexiletine or Control Drugs in the 12-Week, Double-Blind Trials

	Mexiletine N = 430	Quinidine N = 262	Procainamide N = 78	Disopyramide N = 69
Cardiovascular				
Palpitations	4.3	4.6	1.3	5.8
Chest Pain	2.6	3.4	1.3	2.9
Angina/Angina-like Pain	1.7	1.9	2.6	2.9
Increased Ventricular Arrhythmias/PVC's	1.0	2.7	2.6	—
Digestive				
Nausea/Vomiting/Heartburn	39.3	21.4	33.3	14.5
Diarrhea	5.2	33.2	2.6	8.7
Constipation	4.0	—	6.4	11.6
Changes in Appetite	2.6	1.9	—	—
Abdominal Pain/Cramps/Discomfort	1.2	1.5	—	1.4
Central Nervous System				
Dizziness/Lightheadedness	18.9	14.1	14.1	2.9
Tremor	13.2	2.3	3.8	1.4
Coordination Difficulties	9.7	1.1	1.3	—
Changes in Sleep Habits	7.1	2.7	11.5	8.7
Weakness	5.0	5.3	7.7	2.9
Nervousness	5.0	1.9	6.4	5.8
Fatigue	3.8	5.7	5.1	1.4
Speech Difficulties	2.6	0.4	—	—
Confusion/Clouded Sensorium	2.6	—	3.8	—
Paresthesias/Numbness	2.4	2.3	2.6	—
Tinnitus	2.4	1.5	—	—
Depression	2.4	1.1	1.3	1.4
Other				
Blurred Vision/Visual Disturbances	5.7	3.1	5.1	7.2
Headache	5.7	6.9	7.7	4.3
Rash	4.2	3.8	10.3	1.4
Dyspnea/Respiratory	3.3	3.1	5.1	2.9
Dry Mouth	2.8	1.9	5.1	14.5
Arthralgia	1.7	2.3	5.1	1.4
Fever	1.2	3.1	2.6	—

Less than 1%: Syncope, edema, hot flashes, hypertension, short-term memory loss, loss of consciousness, other psychological changes, diaphoresis, urinary hesitancy/retention, malaise, impotence/decreased libido, pharyngitis.

An additional group of over 10,000 patients has been treated in a program allowing administration of Mexitil under compassionate use circumstances. These patients were seriously ill with the large majority on multiple drug therapy. Twenty-four percent of the patients continued in the program for one year or longer. Adverse reactions leading to therapy discontinuation occurred in 15% of patients (usually upper gastrointestinal system or nervous system effects). In general, the more common adverse reactions were similar to those in the controlled trials. Less common adverse events possibly related to Mexitil use include:

Cardiovascular System: Syncope and hypotension, each about 6 in 1000; bradycardia, about 4 in 1000; angina/angina-like pain, about 3 in 1000; edema, atrioventricular block/conduction disturbances and hot flashes, each about 2 in 1000; atrial arrhythmias, hypertension and cardiogenic shock, each about 1 in 1000.

Central Nervous System: Short-term memory loss, about 9 in 1000 patients; hallucinations and other psychological changes, each about 3 in 1000; psychosis and convulsions/seizures, each about 2 in 1000; loss of consciousness, about 6 in 10,000.

Digestive: Dysphagia, about 2 in 1000; peptic ulcer, about 8 in 10,000; upper gastrointestinal bleeding, about 7 in 10,000; esophageal ulceration, about 1 in 10,000.

Laboratory: Abnormal liver function tests, about 5 in 1000 patients; positive ANA and thrombocytopenia, each about 2 in 1000; leukopenia (including neutropenia and agranulocytosis), about 1 in 1000; myelofibrosis, about 2 in 10,000 patients.

Other: Diaphoresis, about 6 in 1000; altered taste, about 5 in 1000; salivary changes, hair loss and impotence/decreased libido, each about 4 in 1000; malaise, about 3 in 1000; urinary hesitancy/retention, each about 2 in 1000; hiccups, dry skin, laryngeal and pharyngeal changes and changes in oral mucous membranes, each about 1 in 1000; SLE syndrome, about 4 in 10,000.

Hematology: Blood dyscrasias were not seen in the controlled trials but did occur among the 10,867 patients treated with mexiletine in the compassionate use program: (See PRECAUTIONS). Myelofibrosis was reported in two patients in the compassionate use program; one was receiving long-term thiotepa therapy and the other had pretreatment myeloid abnormalities.

HOW SUPPLIED:
Mexitil® (mexiletine hydrochloride) is supplied in hard gelatin capsules containing 150, 200 or 250 mg of mexiletine hydrochloride in bottles of 100 and individually blister-sealed unit-dose cartons of 100.

Consult package insert before prescribing.

ME-4063

ME-BS-4/87

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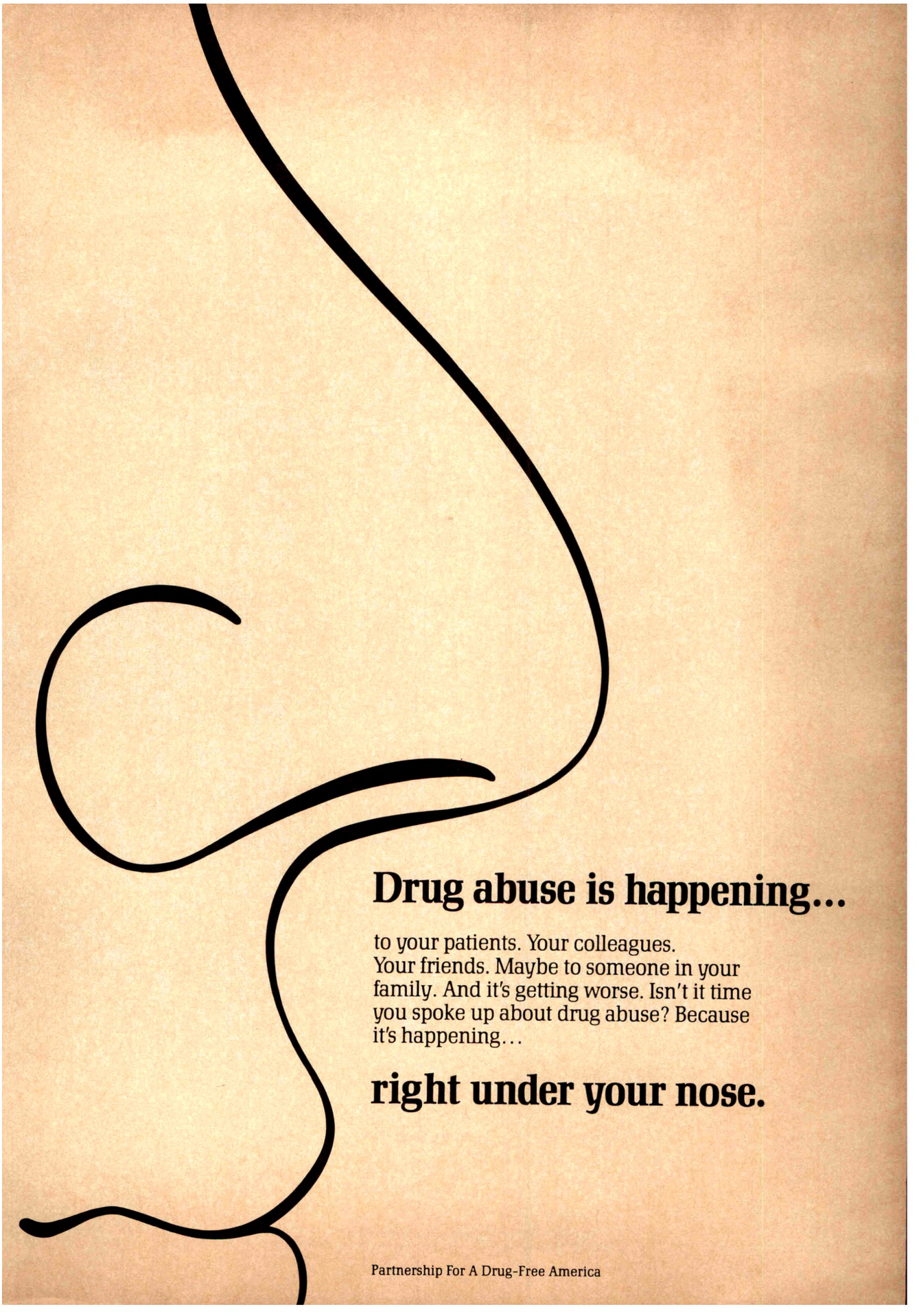
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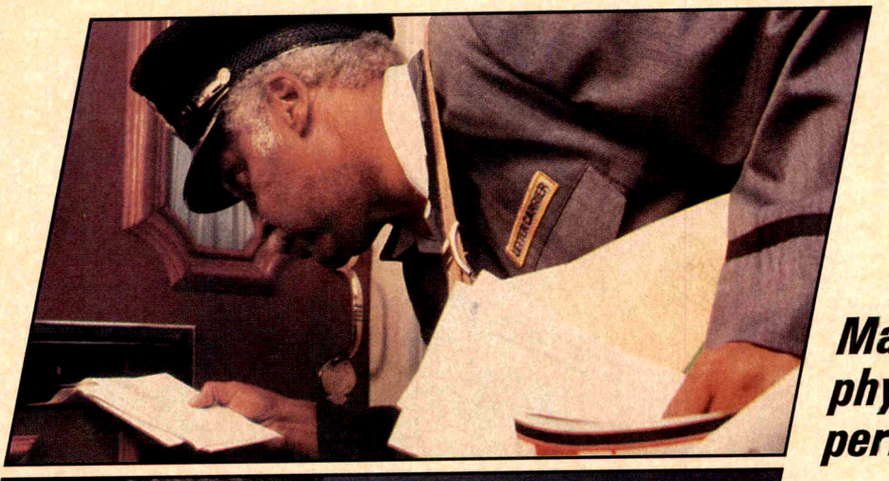
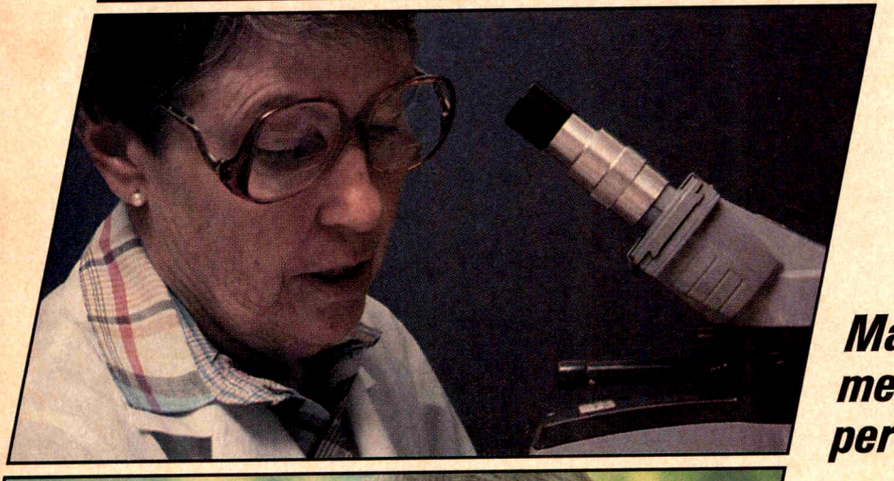


Maintains physical performance



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- *Alpha$_1$ blockers maintain normal hemodynamics during rest and exercise*[1]
- *Seldom causes depression, confusion, loss of alertness*[2]
- *Impotence is rare—incidence equal to placebo*[3]

Significantly decreases total cholesterol*[4]

Effective in younger and older patients, blacks as well as whites[1]

Side effects generally were mild and transient. Dizziness and asthenia were most common. Others reported significantly more frequently than with placebo were nasal congestion, peripheral edema, somnolence, nausea, palpitations, and blurred vision. Incidence of syncope (1.0%) was not significantly different from placebo.

** HYTRIN is not indicated for the treatment of hyperlipidemia.*

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Please see adjacent page for Brief Summary of prescribing information.

HYTRIN®

(terazosin hydrochloride tablets)

Brief Summary

CLINICAL PHARMACOLOGY: Pharmacodynamics: Clinical studies of terazosin used in once-a-day (majority) and b.i.d regimens with total doses usually in the range of 5-20mg/day, in patients with mild or moderate hypertension. Because terazosin, like all alpha antagonists, can cause large falls in blood pressure after the first dose or first few doses, the initial dose was 1mg in virtually all studies, with subsequent titration to a specified fixed dose or titration to a specified blood pressure end point.

Blood pressure responses were measured at the end of the dosing interval (usually 24 hrs.) and effects were shown to persist throughout the interval, with usual supine responses 5-10mmHg systolic and 3.5-8mmHg diastolic greater than placebo. The responses in the standing position tended to be somewhat larger, although this was not true in all studies. The magnitude of blood pressure responses was similar to prazosin and less than hydrochlorothiazide (in a single study). In measurements 24 hrs. after dosing, heart rate was unchanged.

Limited measurements of peak response (2-3 hrs. after dosing) during chronic terazosin administration indicate that it is more than twice the trough (24 hr.) response, suggesting some attenuation of response at 24 hrs., presumably due to a fall in blood terazosin concentrations at the end of the dose interval. This explanation is not established with certainty and is not consistent with the similarity of blood pressure response to once-a-day and b.i.d. dosing. With the absence of an observed dose-response relationship over a range of 5-20mg, i.e., if blood concentrations fall to the point of providing less than full effect at 24 hrs., a shorter dosing interval or larger dose should lead to increased response. Measure blood pressure (BP) at the end of the dose interval; if response is not satisfactory, patients may be tried on a larger dose or b.i.d. regimen. The latter should be considered if side effects, such as dizziness, palpitations, or orthostatic complaints, are seen within a few hours after dosing.

The greater BP effect associated with peak plasma concentrations (first few hours after dosing) appears somewhat more position-dependent (greater in the erect position) than the effect of terazosin at 24 hrs. In the erect position there is a 6-10 bpm increase in heart rate in the first few hours after dosing. During the first 3 hrs. after dosing 12.5% of patients had a systolic pressure fall of 30mmHg or more from supine to standing, or standing systolic pressure below 90mmHg with a fall of at least 20mmHg, compared to 4% of a placebo group.

INDICATIONS AND USAGE: Indicated for the treatment of hypertension.

CONTRAINDICATIONS: None known.

WARNINGS: Syncope and "First-dose" Effect: Terazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially postural hypotension, and syncope in association with the first dose or first few doses. A similar effect may occur if therapy is interrupted for more than a few doses. Syncope has been reported with other alpha-adrenergic blocking agents in association with rapid dosage increases or introduction of another antihypertensive drug. Syncope may be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by severe supraventricular tachycardia with heart rates of 120-160 bpm.

To decrease the likelihood of syncope or excessive hypotension, always initiate treatment with a 1mg dose at bedtime. The 2mg and 5mg tablets are not indicated as initial therapy. Increase dosage slowly, and add additional antihypertensive agents with caution. Caution patients to avoid situations where injury could result if syncope occurs during initiation of therapy.

In early studies, where increasing single doses up to 7.5mg were given at 3 day intervals, tolerance to the first dose phenomenon did not necessarily develop and the "first dose" effect was observed at all doses. Syncopal episodes occurred in 3 of 14 subjects given doses of 2.5, 5, and 7.5mg, which are higher than the recommended initial dose. Severe orthostatic hypotension (BP 50/0mmHg) was seen in two others and dizziness, tachycardia, and lightheadedness occurred in most subjects. These adverse effects all occurred within 90 min. of dosing.

In multiple dose clinical trials involving nearly 2000 patients, syncope was reported in about 1% of patients, in no case severe or prolonged, and was not necessarily associated with early doses.

If syncope occurs, place patient in recumbent position and treat supportively. There is evidence that the orthostatic effect of terazosin is greater, even in chronic use, shortly after dosing.

PRECAUTIONS: *General: Orthostatic Hypotension:* While syncope is the most severe orthostatic effect of terazosin, other symptoms of lowered BP, such as dizziness, lightheadedness and palpitations, are more common, occurring in 28% of patients in clinical trials. Patients with occupations in which such events represent potential problems should be treated with particular caution.

Information for Patients: Make aware of possibility of syncopal and orthostatic symptoms, especially at initiation of therapy, and to avoid driving or hazardous tasks for 12 hrs. after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. Caution to avoid situations where injury could result should syncope occur during initial therapy. Advise to sit or lie down when symptoms of lowered BP occur and to rise carefully from a sitting or lying position. Bothersome dizziness, lightheadedness, or palpitations should be reported to physician.

Tell patients that drowsiness or somnolence can occur, requiring caution in people who must drive or operate heavy machinery.

Laboratory Tests: Small but statistically significant decreases in hematocrit, hemoglobin, WBC, total protein and albumin were observed in clinical trials. The magnitude of decreases did not worsen with time. These findings suggest the possibility of hemodilution.

Drug Interactions: In controlled trials, terazosin was added to diuretics, and several beta-adrenergic blockers; no unexpected interactions were observed. Terazosin has also been used concomitantly without interaction in at least 50 patients on the following: 1) analgesic/anti-inflammatory (acetaminophen, aspirin, codeine, ibuprofen, indomethacin); 2) antibiotics (erythromycin, trimethoprim and sulfamethoxazole); 3) anticholinergic/sympathomimetics (phenylephrine HCl, phenylpropanolamine HCl, pseudoephedrine HCl); 4) antigout (allopurinol); 5) antihistamines (chlorpheniramine); 6) cardiovascular agents (atenolol, hydrochlorothiazide, methyclothiazide, propranolol); 7) corticosteroids; 8) gastrointestinal agents (antacids); 9) hypoglycemics; 10) sedatives and tranquilizers (diazepam).

Carcinogenesis, Mutagenesis, Impairment of Fertility: HYTRIN was devoid of mutagenic potential when evaluated *in vivo* and *in vitro*.

HYTRIN, administered in feed to rats at doses of 8, 40, and 250mg/kg/day for 2 yrs., was associated with a statistically significant increase in benign adrenal medullary tumors of male rats exposed to the 250mg/kg dose. This dose is 695 X max. recommended human dose (20mg/55kg). Female rats were unaffected. HYTRIN was not oncogenic in mice when administered in feed for 2 yrs. at a maximum tolerated dose of 32mg/kg/day.

The absence of mutagenicity in a battery of tests, of tumorigenicity of any cell type in the mouse carcinogenicity assay, of increased total tumor incidence in either species, and of proliferative adrenal lesions in female rats, suggests a male rat species-specific event. Numerous other diverse pharmaceutical and chemical compounds have been associated with these tumors in male rats without supporting evidence for carcinogenicity in man.

Effects on fertility were assessed in a standard fertility/reproductive performance study in which male and female rats were administered oral doses of 8, 30 and 120mg/kg/day. Four of 20 male rats given 30mg/kg and 5 of 19 male rats given 120mg/kg failed to sire a litter. Testicular weights and morphology were unaffected. Vaginal smears at 30 and 120mg/kg/day appeared to contain less sperm than smears from control matings and good correlation was reported between sperm count and subsequent pregnancy.

Oral use for 1 or 2 yrs. elicited a statistically significant increase in testicular atrophy in rats exposed to 40 and 250mg/kg/day, but not in rats exposed to 8mg/kg/day (> 20 X max. recommended human dose). Testicular atrophy was observed in dogs dosed with 300mg/kg/day (> 800 X max. recommended human dose) for 3 months but not after 1 yr. when dosed with 20mg/kg/day. This lesion has also been seen with Minipress®.

Pregnancy: Teratogenic effects: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women and the safety of terazosin in pregnancy has not been established. HYTRIN is not recommended during pregnancy unless potential benefit justifies potential risk to mother and fetus.

Nonteratogenic effects: In a peri- and post-natal development study in rats, significantly more pups died in the group dosed with 120mg/kg/day (> 300 X max. recommended human dose) than in the control group during the 3-week post partum period.

Nursing Mothers: It is not known whether terazosin is excreted in breast milk; therefore, exercise caution when administering terazosin to a nursing woman.

Pediatric Use: Safety and effectiveness have not been determined.

ADVERSE REACTIONS: The prevalence of adverse reactions has been ascertained from 14 placebo-controlled studies conducted primarily in the U.S. The studies involved once-a-day administration of terazosin as monotherapy or in combination with other antihypertensive agents, at doses ranging from 1 to 40mg. All adverse events reported during these studies were recorded as adverse reactions. Adverse events where the prevalence rate in the terazosin group was at least 5%, where the prevalence rate for the terazosin group was at least 2% and was greater than the prevalence rate for the placebo group, or where the reaction is of particular interest are summarized below. Only asthenia, blurred vision, dizziness, nasal congestion, nausea, peripheral edema, palpitations and somnolence were significantly ($p < 0.05$) more common in patients receiving terazosin than in patients receiving placebo. Other events include **[%TERAZOSIN-%PLACEBO]**, asthenia (11.3%-4.3%), back pain (2.4%-1.2%), blurred vision (1.6%-0%), depression (0.3%-0.2%), dizziness (19.3%-7.5%), dyspnea (3.1%-2.4%), edema (0.9%-0.6%), headache (16.2%-15.8%), impotence (1.2%-1.4%), libido decreased (0.6%-0.2%), nasal congestion (5.9%-3.4%), nausea (4.4%-1.4%), nervousness (2.3%-1.8%), pain-extremities (3.5%-3%), palpitations (4.3%-1.2%), paresthesia (2.9%-1.4%), peripheral edema (5.5%-2.4%), postural hypotension (1.3%-0.4%), sinusitis (2.6%-1.4%), somnolence (5.4%-2.6%), tachycardia (1.9%-1.2%), weight gain (0.5%-0.2%).

Adverse reactions were usually mild or moderate in intensity but sometimes were serious enough to interrupt treatment. Adverse reactions that were most bothersome as judged by being reported as reasons for discontinuation of therapy by at least 0.5% of the terazosin group and being reported more often than in the placebo group **[%TERAZOSIN-%PLACEBO]** are: asthenia (1.6%-0%), blurred vision (0.6%-0%), dizziness (3.1%-0.4%), dyspnea (0.9%-0.6%), headache (1.3%-1%), nasal congestion (0.6%-0%), nausea (0.8%-0%), palpitations (1.4%-0.2%), paresthesia (0.8%-0.2%), peripheral edema (0.6%-0%), postural hypotension (0.5%-0%), somnolence (0.6%-0.2%), syncope (0.5%-0.2%), tachycardia (0.6%-0%).

Additional adverse reactions have been reported, but these are not distinguishable from symptoms that might have occurred in the absence of exposure to terazosin. The following additional adverse reactions were reported by at least 1% of 1987 patients who received terazosin in clinical studies or during marketing experience: abdominal pain, abnormal vision, anxiety, arrhythmia, arthralgia, arthritis, bronchitis, chest pain, cold symptoms, conjunctivitis, constipation, diarrhea, dry mouth, dyspepsia, epistaxis, facial edema, fever, flatulence, flu symptoms, gout, increased cough, insomnia, joint disorder, myalgia, neck pain, pharyngitis, pruritus, rash, rhinitis, shoulder pain, sweating, tinnitus, urinary frequency, urinary tract infection, vasodilation, vomiting.

DOSAGE AND ADMINISTRATION: Dose and dose interval (12 or 24 hrs.) should be adjusted according to BP response.

Initial Dose: 1mg at bedtime. Observe the initial dosing regimen strictly to minimize potential for severe hypotensive effects.

Subsequent Doses: Slowly increase dose to achieve desired BP response. Usual dose range is 1mg to 5mg once a day. Some patients may benefit from doses up to 20mg/day. Doses over 20mg do not appear to provide further BP effect. Doses over 40mg have not been studied. Monitor BP at the end of dosing interval to assure control is maintained. It may be helpful to measure BP 2-3 hrs. after dosing to see if maximum and minimum responses are similar, and to evaluate symptoms which can result from excessive hypotensive response. If response is substantially diminished at 24 hrs. consider an increased dose or b.i.d. regimen. **If administration is discontinued for several days or longer, reinstitute therapy using initial dosing regimen.** In clinical trials, except for the initial dose, the dose was given in the morning.

Use With Other Drugs: Caution should be observed when terazosin is administered concomitantly with other antihypertensive agents (e.g., calcium antagonists) to avoid the possibility of significant hypotension. When adding a diuretic or other antihypertensive agent, dosage reduction and retitration may be necessary.

August, 1987 **Abbott Health Care Products, Inc.** North Chicago, IL 60064 8023854

References: 1. Dzau VJ: Evolution of the clinical management of hypertension; Emerging role of "specific" vasodilators as initial therapy. *Am J Med* 1987;82(suppl 1A):36-43. **2.** Data on file, Abbott Pharmaceuticals. **3.** Mersey JH: Alpha$_1$-blockade in hypertension management. *Prim Cardiol* 1987;13: 93-101. **4.** Hytrin: Product Information Abbott Pharmaceuticals.

CARDIOLOGIST—The University of California, San Francisco and the Central California Faculty Medical Group seek a staff cardiologist to join the teaching faculty at their affiliate, Valley Medical Center of Fresno. Applicants should be board certified or eligible. The scope of practice at VMC includes full invasive and non-invasive cardiology services. Geographic location offers a large population with a variety of cardiological diseases. VMC has 350 active beds and conducts residency training programs in most major clinical disciplines. The central California location offers enjoyable and affordable California living. Competitive salary and benefits. UCSF is an equal opportunity employer. Address inquiries to: Lauren Grayson, M.D., Chief of Cardiology, CCFMG, 2212 N. Winery, #130, Fresno, CA 93703, (209) 252-1835.

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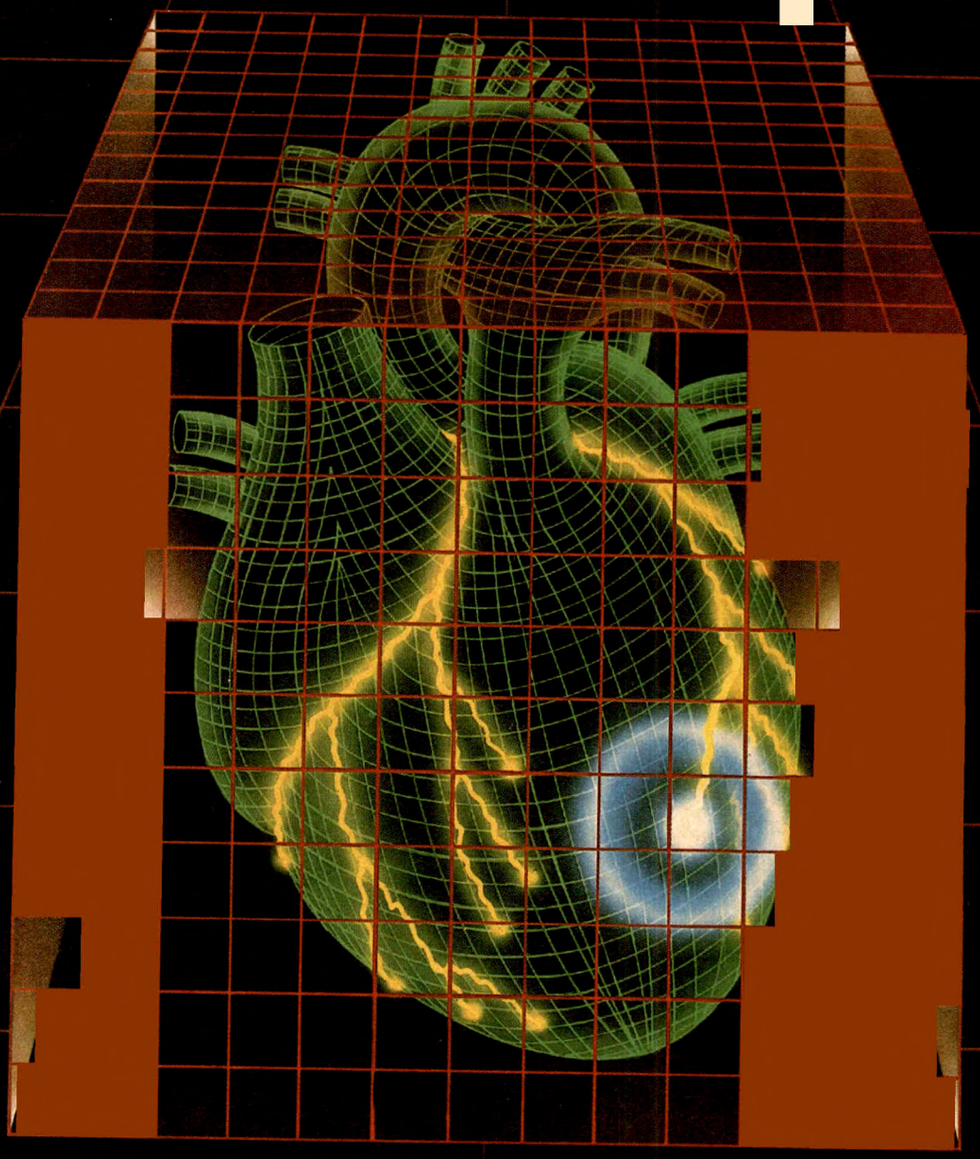

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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure<90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block, atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes).

Warnings: Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction<30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan is used. Calan may occasionally produce hypotension, usually asymptomatic, orthostatic, mild, and controlled by decrease in Calan dose. Elevations of liver enzymes have been reported. Four cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Studies in a small number of patients suggest that concomitant use of Calan and beta-blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, verapamil should be used alone if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with verapamil and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic verapamil treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Concomitant use of verapamil and carbamazepine may produce increased plasma concentrations of free carbamazepine. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd-degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%); elevations of liver enzymes have been reported (see *Warnings*). The following reactions, reported in less than 0.5% of patients, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, macular eruptions, spotty menstruation, ecchymosis, bruising, impotence, gynecomastia, and psychotic symptoms. Overall continuation rate was 94.5% in 1,166 patients. 9/86 • 5W021V4

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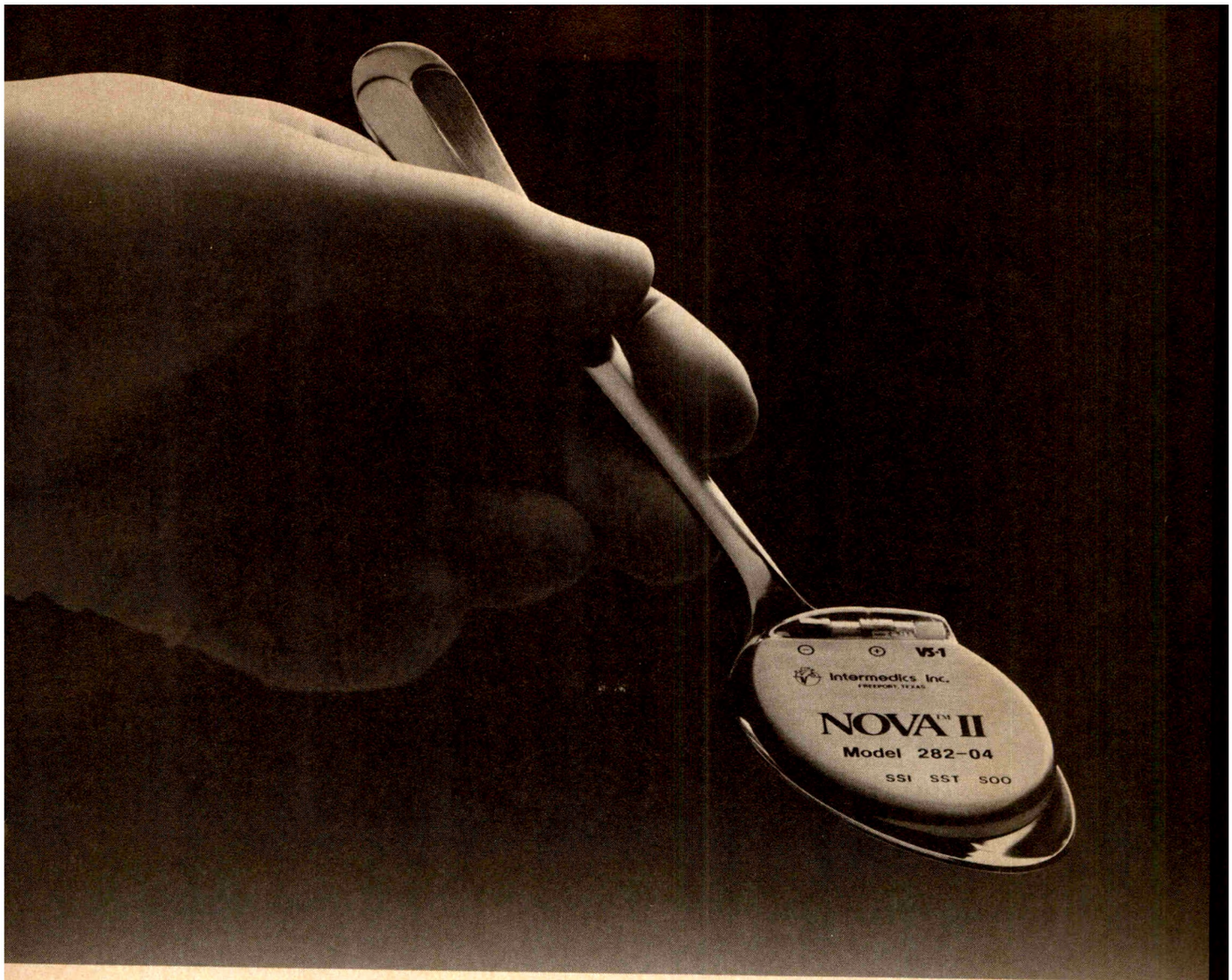

NOVA II. It's the world's smallest pacemaker–weighing just 23 grams and measuring a thin 6.5 mm in width. NOVA II's small size and unique, elliptical shape give new dimensions to patient comfort.

In addition, its new Side-Lock™ lead connector lets you fasten leads quickly and simply, without any special tools.

NOVA™ II gives you the most for your pacing prescription in one small dose.

And whether NOVA II is used in the atrium or ventricle, its full-function programmability, patient and system diagnostics give you the most for your pacing prescription. For more information on how to get single-chamber pacing's biggest advantages in one small dose, call your Intermedics Sales Representative. Or call Intermedics toll-free at 1-800-231-2330. (In Texas, call collect 409-233-8611.) Telex: 4620584 INTL UI.

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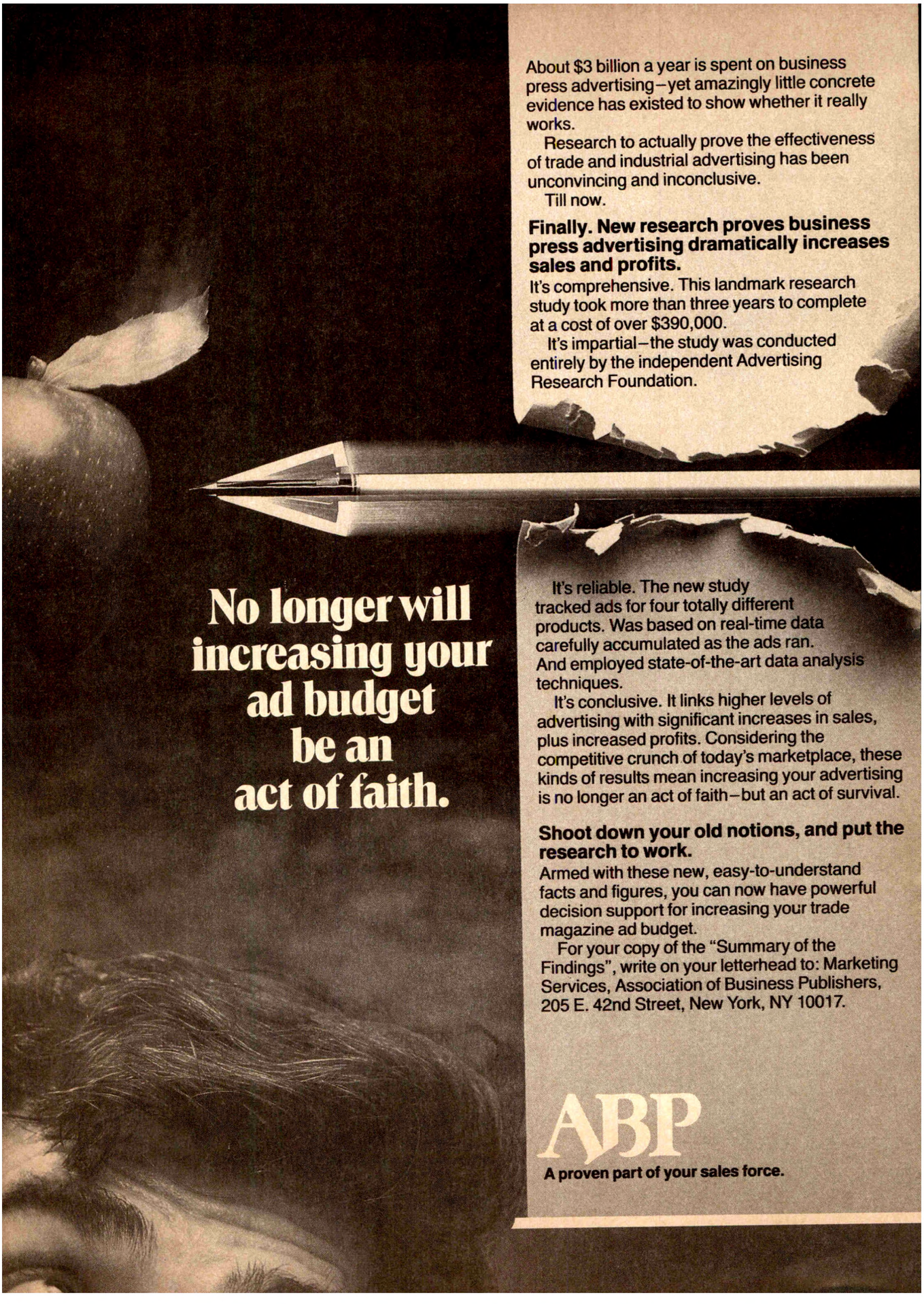

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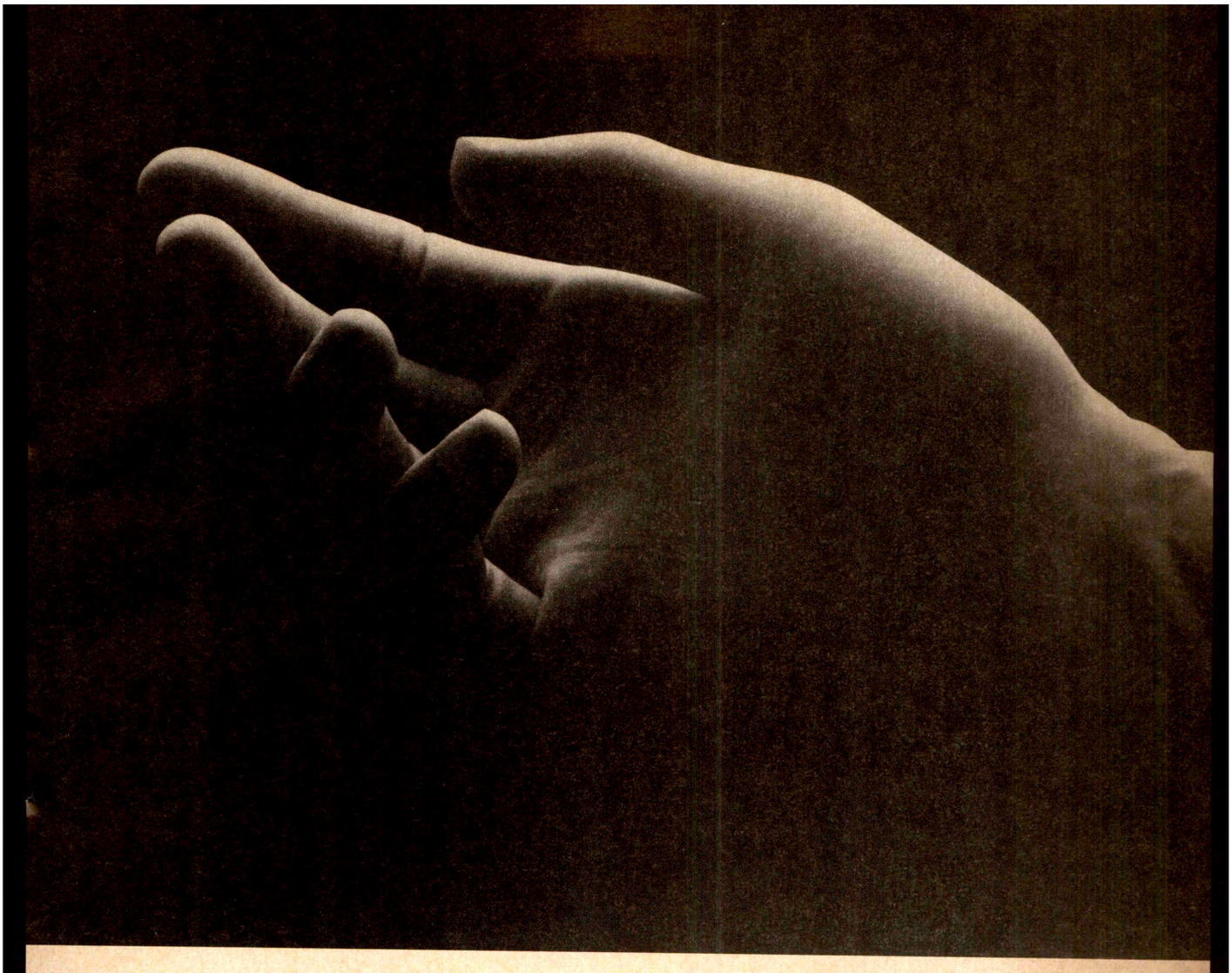

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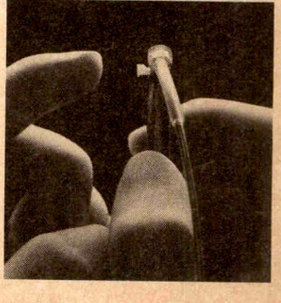

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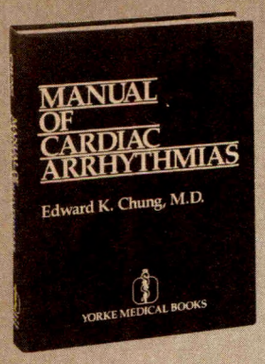

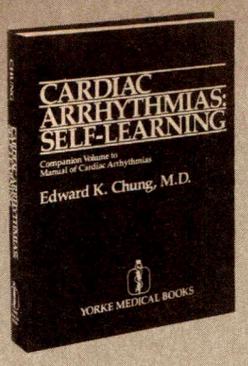

Practical New Books in Cardiology From Yorke Medical Books

For the clinician's working library, the publishers of The American Journal of Cardiology give you only the best

Manual of Cardiac Arrhythmias

BY EDWARD K. CHUNG, M.D., F.A.C.P., F.A.C.C. 0-914316-43-5, November 1985, appx. 324 pp., $30.00

The eminent clinician, professor, and medical writer Dr. Edward K. Chung, has produced the most current "how to" manual on cardiac arrhythmias. The book has been formatted and edited to facilitate its use as a ready reference to up-to-date material on diagnosing and managing arrhythmias commonly seen in daily clinical practice. Its purpose is not to discuss in-depth every aspect of various cardiac rhythm problems, but rather to provide the reader with a concise easy-to-use guide. An invaluable resource for all physicians and allied health professionals seeking to add to their clinical knowledge of a complex topic without the necessity of purchasing a large general text on cardiology.

Table of Contents

- Introductory Remarks
- Anatomy and Electrophysiology
- Diagnostic Approach to Cardiac Arrhythmias
- Sinus Arrhythmias
- Atrial Arrhythmias
- A-V Junctional Arrhythmias
- Intraventricular Conduction Disturbances
- Differential Diagnosis of Tachyarrhythmias
- Aberrant Ventricular Conduction
- Carotid Sinus Stimulation
- Wolff-Parkinson-White Syndrome
- Sick Sinus Syndrome
- Therapeutic Approach to Cardiac Arrhythmias
- Digitalization
- Digitalis Intoxication
- Antiarrhythmic Drug Therapy
- Artificial Cardiac Pacing
- Direct Current Shock
- Cardiopulmonary Resuscitation
- Uncommon Cardiac Arrhythmias

Cardiac Arrhythmias

Self Learning Companion Volume to Manual of Cardiac Arrhythmias

BY EDWARD K. CHUNG, M.D., F.A.C.P., F.A.C.C. 0-914316-46-X, November 1985, appx. 440 pp., $30.00

Conceived by Dr. Chung as a companion volume to Manual of Cardiac Arrhythmias, this book includes 200 cases showing common cardiac arrhythmias frequently encountered in clinical practice.

Interpretation of the ECG training is aided by short case histories. The reverse side of each page gives a full analysis of the interpretation of the tracing, enabling readers to assess their own ECG diagnosis. In the majority of cases, three simultaneous ECG leads (leads V, II, and V_5) recorded by 3-channel ECG equipment, are shown for accurate diagnosis. In addition to the ECG diagnosis, the pertinent clinical significance and therapeutic approach are included in many instances.

The arrangement of the text and illustrations is based upon the author's extensive experience in teaching medical students, house staff, cardiology fellows, cardiac care nurses, and physicians with diversified backgrounds and specialties.

The unique feature of this book, is its practical approach to clinical applications that directly assist readers in the diagnosis and management of their patients.

Contents

- A-V Block
- Intraventricular Block
- Sinus Arrhythmias
- Atrial Arrhythmias
- A-V Junctional Arrhythmias
- Ventricular Arrhythmias
- Differential Diagnosis of Cardiac Arrhythmias
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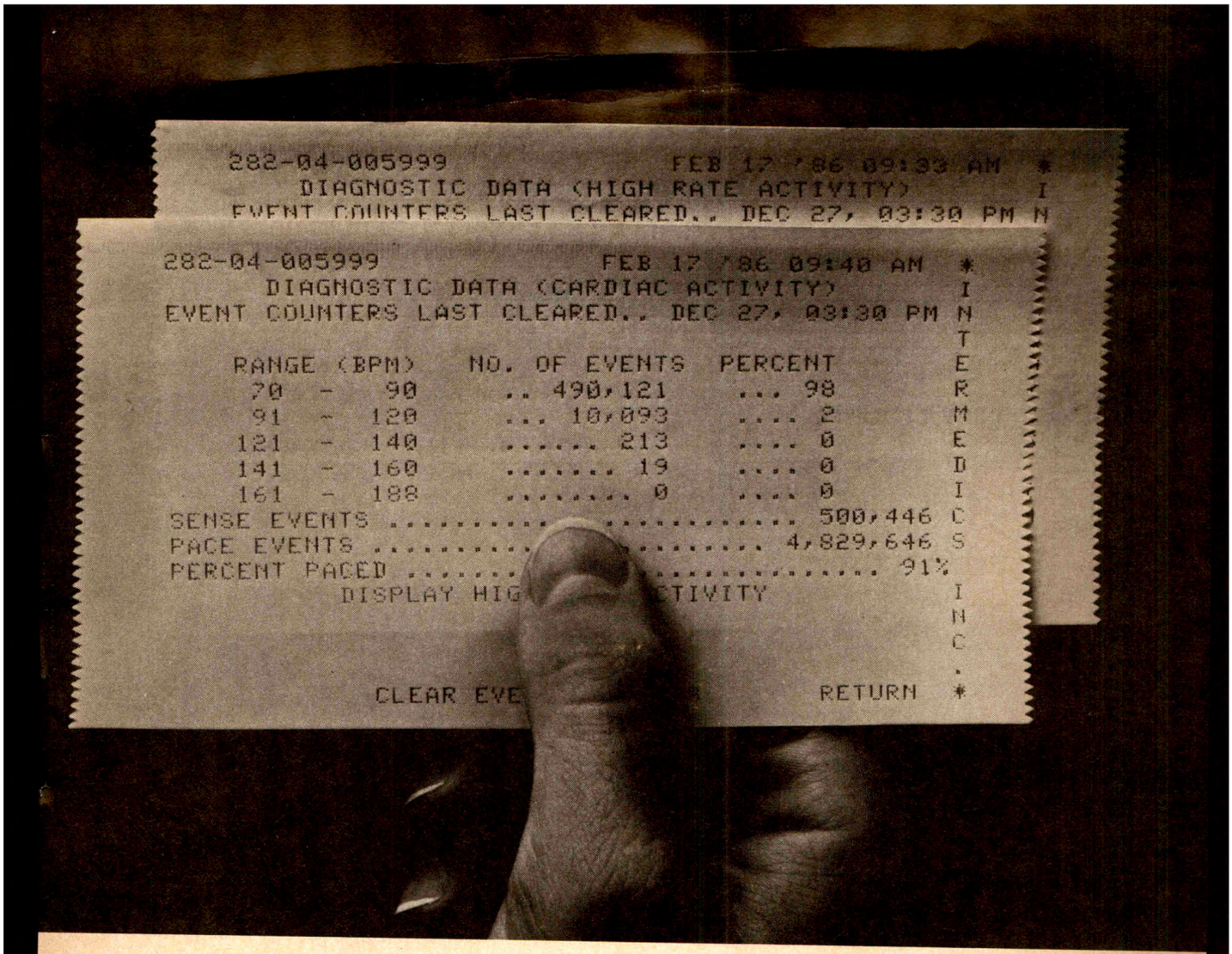
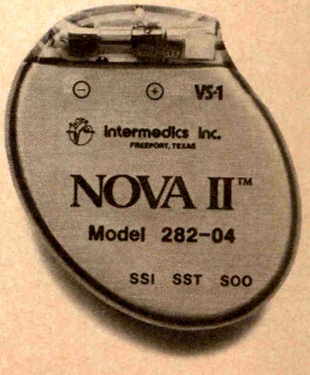


NOVA II's wide range of diagnostic capabilities, including a rate histogram and a high rate event counter, simplify patient follow-up. NOVA II also offers broad programming flexibility so you can titrate pacing parameters in very fine increments to better meet your patient's need.

All this comes in the world's smallest pacemaker, with the simplest lead connector system available today.

Intermedics NOVA™ II offers you more diagnostic data than any other single-chamber pacemaker.

Shown actual size.



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The publisher is not responsible for any errors or omissions.

Nitro-Dur II

NOW EVEN ITS NAME IS SIMPLER.

Since we introduced Nitro-Dur II, it has remained, in our opinion, the easiest patch to open, handle, and apply. But now, it's also becoming easier to prescribe.

Key Pharmaceuticals, Inc., has deleted the Roman numeral "II" from the name of the transdermal nitroglycerin system formerly known as "Nitro-Dur II." In all other respects, the product will remain identical to the Nitro-Dur II system you have been prescribing.

The original large, white Nitro-Dur system is being discontinued. From now on, prescriptions you write for either "Nitro-Dur" or "Nitro-Dur II" will be filled with the renamed Nitro-Dur product.

Key Pharmaceuticals has retained the name Nitro-Dur because of its wide recognition among patients and health care professionals. Now you can simply write Nitro-Dur, and be confident that patients are getting the most advanced, easy-to-use nitroglycerin patch design available today.

Nitro-Dur®
(nitroglycerin)
Transdermal Infusion System
Easy to open...apply...remove.

Formerly named Nitro-Dur II.

Please see next page for summary of prescribing information.
All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA.
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Nitro-Dur®
(nitroglycerin)
Transdermal Infusion System
Easy to open...apply...remove.

Formerly named Nitro-Dur II.

BRIEF SUMMARY

INDICATIONS AND USAGE: This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia.

WARNINGS: The NITRO-DUR system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced or use of the product discontinued.

NITRO-DUR is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with NITRO-DUR. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NITRO-DUR is administered to a nursing woman.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing NITRO-DUR therapy. If headache persists, the NITRO-DUR dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the NITRO-DUR dosage should be reduced or use of the product discontinued.

CAUTION: Federal law prohibits dispensing without prescription.
Revised 09/87 EDP #I030160
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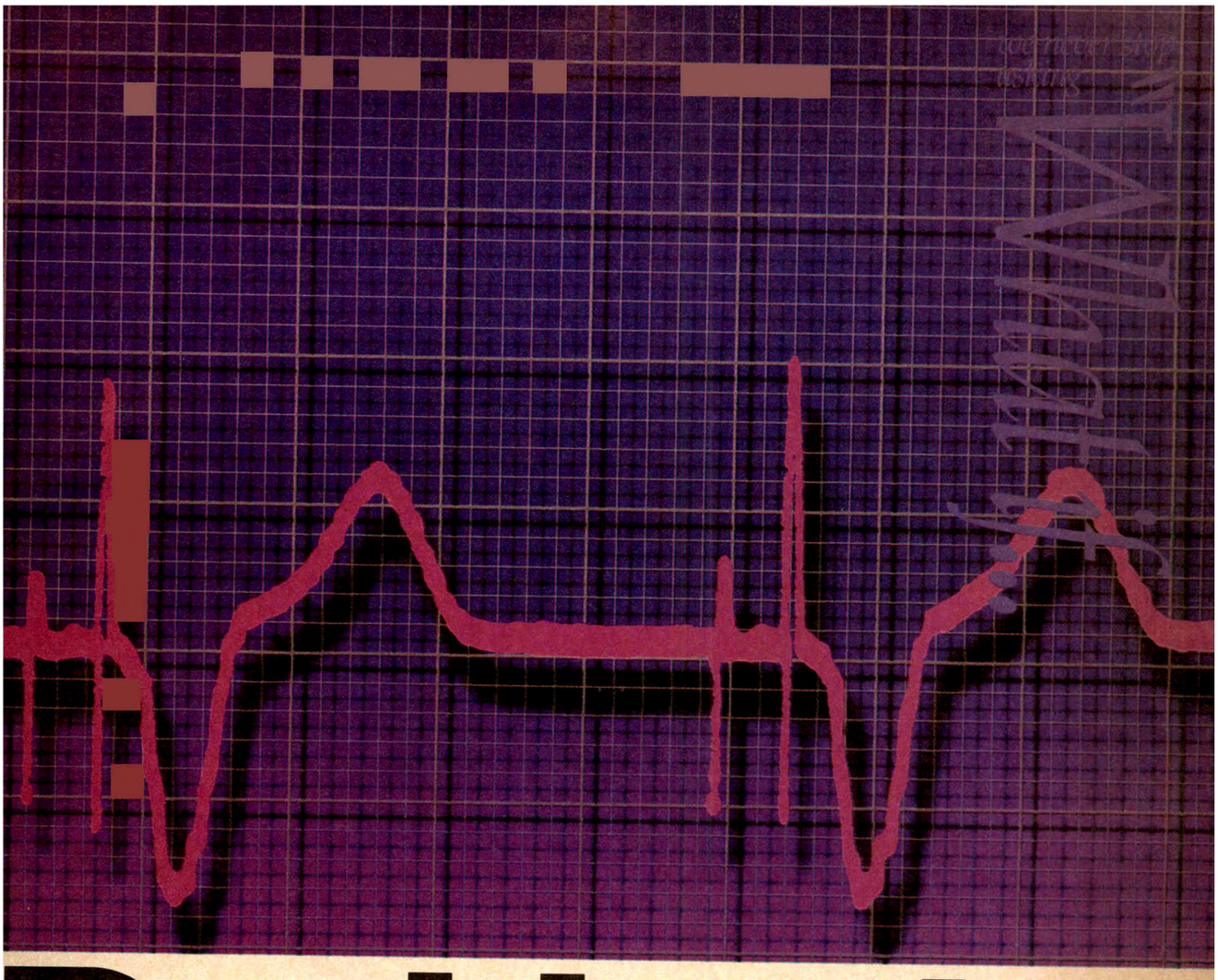

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Introducing dual-chamber paced patient arrhythmia monitoring from HP.

When it comes to arrhythmia monitoring, Hewlett-Packard does it again. And again. The latest breakthrough—an algorithm so accurate it eliminates excessive false alarms for dual-chamber paced patients.

Through improved beat classification, HP's new algorithm provides greater accuracy. More sensitive detection of VPBs and ventricular rhythms. Less double counting. And more accurate recognition of true QRS complexes. Regardless of pacemaker type.

What's more, coupled with the reduced false alarm rate, the HP 78720's latest software upgrade provides you with more comprehensive information and clearer documentation for patient assessment.

The bottom line? Whether you're monitoring non-paced, single or dual-chamber paced patients, the HP 78720's enhanced algorithm gives you the confidence and accuracy you need.

Add HP reliability. Service. Training. Support. And a commitment to innovative upgrades. Hewlett-Packard continues to set the pace in arrhythmia monitoring.

For further information on the HP 78720 and its full range of capabilities, contact your local HP representative. Or return the coupon today.

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☐ Please send me a copy of the HP brochure, "Even better arrhythmia monitoring."

☐ Please contact me for a demonstration of the HP 78720.

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Title:

Hospital:

Address:

City: State: Zip: AJC 4/1/88

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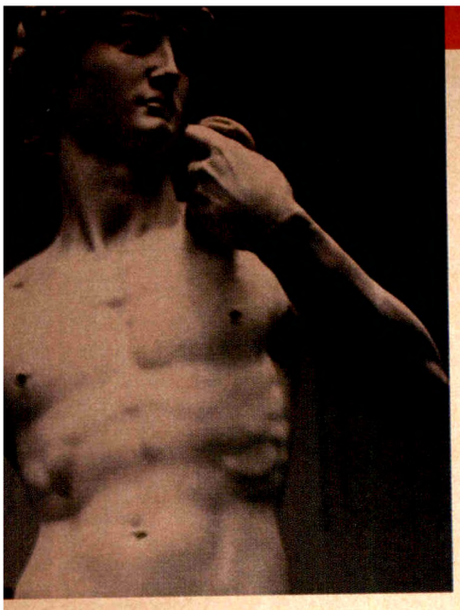

ENKAID®
(encainide HCl)

An alternative to classic antiarrhythmic therapy

For symptomatic non-sustained V-Tach and frequent PVCs

Treatment of symptomatic PVCs and non-sustained V-Tach should be reserved for patients in whom, in the opinion of the physician, the benefits of antiarrhythmic therapy outweigh the risks (e.g., proarrhythmia).

For documented life-threatening arrhythmias

Therapy should be initiated in the hospital for patients with sustained V-Tach and is also advisable for patients with a relatively high risk of proarrhythmia and at the time of a dose increase to 200 mg/day or above.

The antiarrhythmic benefits of quinidine,

with fewer non-cardiac side effects

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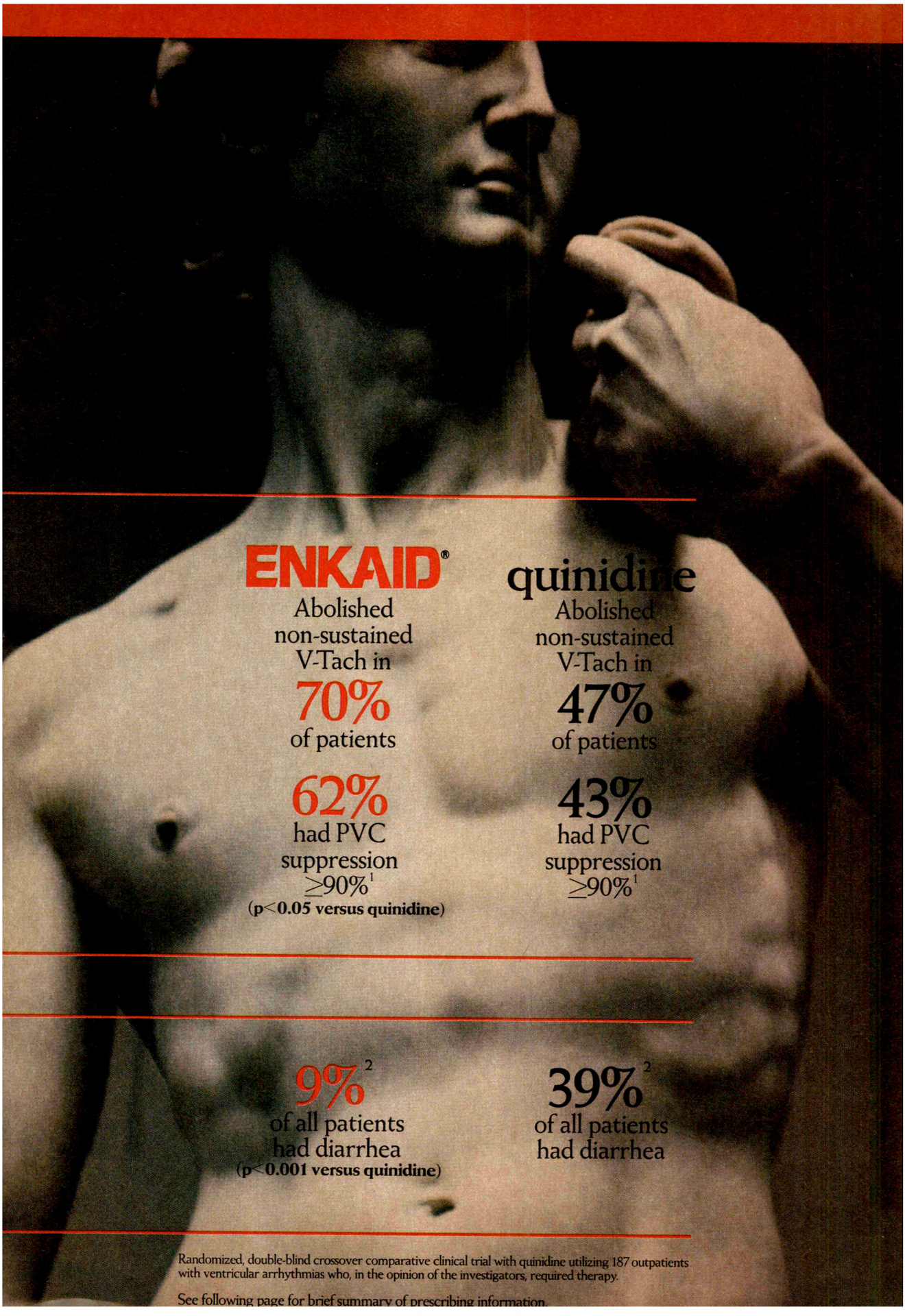
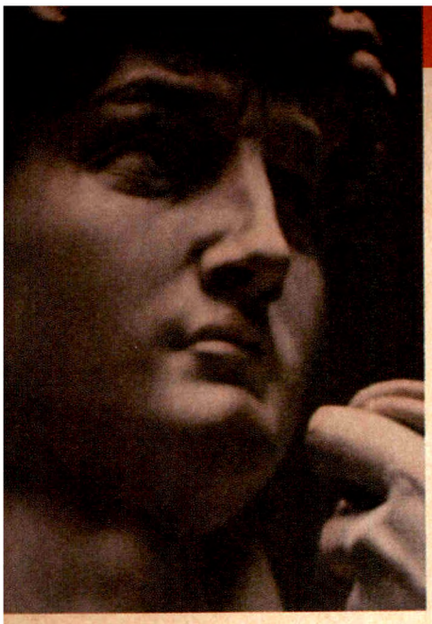


Randomized, double-blind crossover comparative clinical trial with quinidine utilizing 187 outpatients with ventricular arrhythmias who, in the opinion of the investigators, required therapy.

See following page for brief summary of prescribing information.



ENKAID®
(encainide HCl)

Effective with no changes in cardiac performance

- Studies of hemodynamic effects show no changes in:
  - left ventricular ejection fraction
  - cardiac or stroke volume index
  - pulmonary capillary wedge pressure
- Effective even in patients refractory to other antiarrhythmics.

ENKAID® (encainide HCl)

Dosage	Usual Recommendation
Initial dose	25 mg t.i.d.*
First increment (if required)	35 mg t.i.d.*
Second increment (if required)	50 mg t.i.d.*
Maximum recommended	50 mg q.i.d.**

*approximately q8h **approximately q6h

Initiate therapy at lowest dosage and increase gradually. Allow 3 to 5 days between dosing increments.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

INDICATIONS AND USAGE

ENKAID is indicated for the treatment of documented life-threatening arrhythmias, such as sustained ventricular tachycardia.

ENKAID is also indicated for the treatment of patients with symptomatic non-sustained ventricular tachycardia and frequent premature ventricular complexes. Because of the proarrhythmic effects of ENKAID, its use in these less severe arrhythmias should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

For patients with sustained ventricular tachycardia, ENKAID, like other antiarrhythmics should be initiated in the hospital. Hospitalization is also advisable for other patients with a relatively high risk of proarrhythmia including patients with symptomatic congestive heart failure, cardiomyopathy or non-sustained ventricular tachycardia, depending on their cardiac status and underlying cardiac disease. Patients should also be hospitalized at the time of a dose increase to 200 mg per day or above (see **DOSAGE AND ADMINISTRATION**).

The effects of ENKAID in patients with a recent acute myocardial infarction and in patients with supraventricular arrhythmias have not been adequately studied.

As is the case for other antiarrhythmic agents, there is no evidence from controlled trials that the use of ENKAID favorably affects survival or the incidence of sudden death.

CONTRAINDICATIONS

ENKAID is contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. ENKAID is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS

Proarrhythmia

ENKAID, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase frequency of PVCs to the development of more severe ventricular tachycardia; e.g., tachycardia that is more sustained or more resistant conversion to sinus rhythm, with potentially fatal consequences.

In patients with malignant arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhyth disorder from drug induced worsening, so the following occurrence rates must be considered approximations.

Overall, in clinical trials with ENKAID about 10% of all patients had proarrhythmic events, about 6% of them representing new or worsen ventricular tachycardia. Provocation or aggravation occurred most frequently in patients who had a history of sustained ventricular tachycard (12% of such patients), cardiomyopathy (16%), congestive heart failure (12%) or sustained ventricular tachycardia with cardiomyopathy congestive heart failure (17%). The incidence of proarrhythmic events in patients without ventricular tachycardia or overt manifestations clinical heart disease ranged from 3 to 4%. Proarrhythmia occurred least frequently in patients with no known structural heart disea Age, sex, baseline ECG intervals, or ECG changes caused by ENKAID were not predictive of the occurrence of proarrhythmia.

A review of deaths in clinical trials indicates that about 1% of patients might have died of a possible proarrhythmic effect of ENKA virtually all of them patients with a history of ventricular tachycardia. In most cases patients had a history of sustained ventricular tachycard or ventricular fibrillation.

Proarrhythmic events occurred most commonly during the first week of therapy and were much more common when doses exceed 200 mg/day. Initiating therapy at 75 mg/day combined with gradual dose adjustment reduced the risk of proarrhythmia (See DOSAGE A ADMINISTRATION).

Congestive Heart Failure

New or worsened congestive heart failure (CHF) attributed to ENKAID occurred infrequently (< 1%); nevertheless, ENKA should be used cautiously in patients with CHF or congestive cardiomyopathy.

Electrolyte Disturbances

Hypokalemia or hyperkalemia may alter the effects of Class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalem should be corrected before administration of ENKAID.

Sick Sinus Syndrome—(Bradycardia-Tachycardia Syndrome)

ENKAID should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bra cardia, sinus pause, or sinus arrest.

Electrocardiographic Changes

ENKAID slows conduction and consequently produces dose related changes in the PR and QRS intervals. The interva increase in a linear manner at doses from 30 to 225 mg/day. There is no consistent change in JT. The QTc interval increased, but only to the extent of the increase in QRS interval.

Clinically significant changes in cardiac conduction have been observed. Sinus bradycardia, sinus pause, or sinus arre occurred in 1% of the patients and prolongation of QRS interval to greater than/or equal to 0.20 sec developed in about 7 of the patients. The incidence of second- or third-degree AV block was less, 0.5% and 0.2% respectively.

Effects on Pacemaker Thresholds

The safety of ENKAID in patients with permanently implanted programmable pacemakers has been established in a sm (10 patient) study which evaluated the effects of increasing doses on pacemaker thresholds. ENKAID has a limited potent for increasing pacemaker thresholds. Only one subject had a clinically significant change that would require pacemaker programming and that occurred only at the highest dose tested (75 mg t.i.d.). These effects were reversed when the drug w discontinued. It is advisable to establish pacemaker threshold prior to encainide administration and at regular intervals duri therapy. Reprogramming of multiprogrammable pacemakers may be required to increase voltage or pulse width. ENKA should not be administered to patients with existing poor thresholds or non-programmable pacemakers unless suitat pacing rescue is available. In addition to possible rise in pacing threshold, ENKAID may suppress ventricular escape rhythr

PRECAUTIONS

Drug Interactions

In prospective studies single and multiple doses of ENKAID have had no significant effect on serum digoxin levels. Likewi combined digoxin/ENKAID therapy has been administered without adverse effects.

Experience has indicated no obvious problems with the combined use of ENKAID and other antiarrhythmic age diuretics, beta blockers or calcium channel blockers. However, because of possible additive pharmacologic effects, caut is indicated when ENKAID is used with another antiarrhythmic agent or any other drug that affects cardiac conducti

Cimetidine (300 mg q.i.d.) increases plasma concentrations of encainide and its active metabolites. Although no clinica

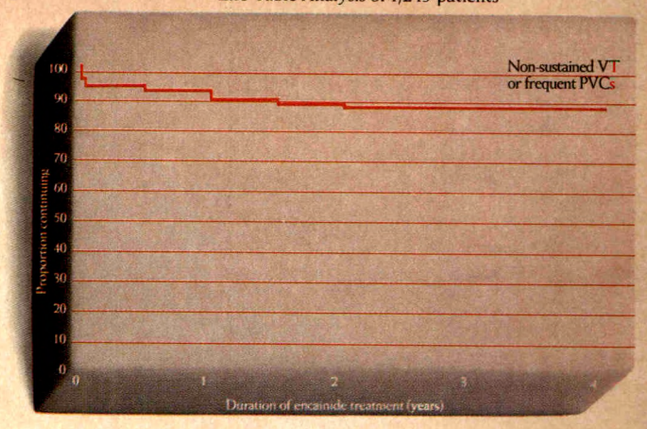
Well tolerated in long-term therapy

■ Few discontinuations due to side effects even after 4 years.

The most serious side effects of Enkaid are dizziness and blurred vision. In clinical studies with Enkaid, about 10% of patients had proarrhythmic events, occurring most frequently in patients with sustained ventricular tachycardia or underlying heart disease.

See brief summary for more information on Enkaid's side effects in life-threatening arrhythmias. Hospitalization is recommended in a facility with cardiac monitoring capabilities for patients with sustained V-Tach, sinus node dysfunction, cardiomyopathy and/or CHF, or at the time of a dose increase to 200 mg/day or above.

Discontinuations due to side effects[3]
Life Table Analysis of 1,245 patients



ENKAID®
(encainide HCl)

An alternative to classic antiarrhythmic therapy

significant consequences have been reported, caution should be utilized when the two drugs are administered simultaneously. ENKAID dosage should be reduced if cimetidine is to be given to a patient taking ENKAID.

In vitro binding studies with several drugs that may be administered concomitantly have not revealed any significant alteration in the protein binding of encainide, ODE, or MODE; nor did high concentrations of encainide and its metabolites alter the binding of the other medications including such highly protein bound drugs as warfarin.

Hepatic Impairment
Patients with hepatic impairment have a significantly reduced rate of elimination of encainide, probably as a consequence of decreased metabolism to ODE and MODE; serum concentrations of ODE and MODE, however, are little altered. There is insufficient experience to be certain about the need for alterations in the dose and/or dosing interval of ENKAID in patients with hepatic disease, but it is prudent to increase doses cautiously.

Renal Impairment
Limited data suggest that reduction in the elimination of encainide and its active metabolites ODE and MODE in patients with severe renal impairment (serum creatinine >3.5 mg/dl or creatinine clearance of less than 20 ml/min) results in significant accumulation of metabolites and, to a lesser degree, encainide. In such patients therapy with ENKAID should be initiated with a single daily dose of 25 mg. If needed the dose may be increased to 25 mg b.i.d. after at least 7 days, and again to 25 mg t.i.d. after an additional 7 days if necessary. Doses above 150 mg per day are not recommended. Consideration should be given to reducing ENKAID dosage if renal function deteriorates significantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have been performed by the oral route in rats and mice at doses up to 30 mg/kg/day and 135 mg/kg/day, respectively. No drug-related increase in tumor incidence was observed. Bacterial and mammalian mutagenicity tests with encainide have been negative. No reduction in fertility occurred in rats at oral doses up to 14 mg/kg/day. Fertility was reduced when both male and female rats received oral doses of 28 mg/kg/day (approximately 13 times the average human dose) prior to mating; there was no reduction with treatment of each sex separately at the same dose.

Pregnancy Category B
Reproduction studies have been performed in rats and rabbits at doses up to 13 and 9 times the average human dose respectively and have revealed no evidence of harm to the fetus due to encainide. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Encainide is excreted in the milk of laboratory animals and has been reported to be present in human milk. Although no overt postnatal effects were observed in the postnatal phase of the rodent reproduction studies, other than decreased weight at the highest dose of 28 mg/kg/day (13 times human dose), the potential for serious adverse reactions in nursing infants from ENKAID is unknown. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and effectiveness of ENKAID in children less than 18 years of age have not been established.

ADVERSE REACTIONS
The most serious adverse reactions reported for ENKAID are the provocation or aggravation of ventricular arrhythmias (See **WARNINGS**). These occurred during the course of the clinical research program in about 10% of the patients who received a wide range of doses under a variety of circumstances. In some cases this resulted in the development of sustained ventricular tachycardia or ventricular fibrillation.

Only 0.4% of patients discontinued ENKAID therapy due to congestive heart failure or related causes. Second- or third-degree AV block developed in 0.5% and 0.2% of the patients respectively. Sinus bradycardia, sinus pause or sinus arrest occurred in 1% of the patients. There have been rare reports of elevated serum liver enzymes (alkaline phosphatase, serum transaminases), hepatitis, and jaundice; in which a relation to encainide is possible and there has been one instance of a rechallenge-confirmed elevation of transaminases. There have also been rare reports of elevated blood glucose levels or of increased insulin requirements in diabetic patients. Although no cause and effect relationship has been established, caution is advised in patients who develop unexplained jaundice or signs of hepatic dysfunction or hyperglycemia and consideration should be given to discontinuing therapy.

In premarketing evaluations 2400 subjects were exposed to ENKAID, of whom more than 500 were maintained on drug for two years or longer. Adverse events were sufficiently troublesome to cause discontinuation in about 7% of the patients participating in premarketing clinical trials. The most frequently reported adverse events are dizziness, blurred or abnormal vision, and headache.

The most common adverse events reported by at least 3% of patients in controlled clinical trials, occurring at frequencies greater than those seen for patients on placebo, are chest pains, death, headache, lower extremity pain, proarrhythmia, abdominal pain, constipation, diarrhea, dry mouth, dyspepsia, nausea, dizziness, insomnia, somnolence, abnormal/blurred vision, and tinnitus.

OVERDOSAGE
Intentional or accidental overdosages with ENKAID have resulted in death.

Signs, Symptoms, and Laboratory Findings Associated with an Overdosage of the Drug
Overdosage with ENKAID may produce excessive widening of the QRS complex and QT interval and AV dissociation. Hypotension, bradycardia and finally asystole may develop. A variety of conduction disturbances may be observed. Convulsions have occurred in one case of intentional overdosage.

Oral LD_{50} of the Drug in Animals
The acute, oral LD_{50} values for encainide are estimated to be 80 mg/kg in the mouse and 59 mg/kg in the rat.

Recommended General Treatment Procedures
In the event of overdosage with ENKAID patients should be hospitalized and provided with cardiac monitoring and advanced life support systems. No specific antidote for ENKAID has been identified; however, one report has suggested hypertonic sodium bicarbonate may be useful in managing the cardiac toxicity associated with an ENKAID overdosage. Acute overdosages should be treated by gastric lavage followed by activated charcoal. Treatment of overdosage should be supportive.

DOSAGE AND ADMINISTRATION
As with other antiarrhythmic agents, ENKAID therapy in patients with sustained ventricular tachycardia should be initiated in a hospital setting with facilities for cardiac rhythm monitoring. Hospitalization is also recommended for patients with sinus node dysfunction or cardiomyopathy and/or congestive heart failure even if there is no history of sustained ventricular tachycardia, and at the time of a dose increase to 200 mg per day or above.

Dosages of ENKAID should be adjusted gradually allowing 3 to 5 days between dosing increments.

HOW SUPPLIED
Capsules, 25 mg, green and yellow hard gelatin capsule imprinted with ENKAID, 25 mg, Bristol and 732.
NDC0087-0732-41 Bottles of 100.
NDC0087-0732-42 Cartons of 100 Unit Dose.
Capsules, 35 mg, green and orange hard gelatin capsule imprinted with ENKAID, 35 mg, Bristol and 734.
NDC0087-0734-41 Bottles of 100.
NDC0087-0734-42 Cartons of 100 Unit Dose.
Capsules, 50 mg, green and brown hard gelatin capsules imprinted with ENKAID, 50 mg, Bristol and 735.
NDC0087-0735-41 Bottles of 100.
NDC0087-0735-42 Cartons of 100 Unit Dose.

U.S. Pat. No. 3,931,195

References:
1. Rinkenberger RL, Naccarelli GV, Dougherty AH: New antiarrhythmic agents: Part X—Safety and efficacy of encainide in the treatment of ventricular arrhythmias. *Practical Cardiol* 1987;13(3):112.
2. Morganroth J, Somberg JC, Pool PE, et al: Comparative study of encainide and quinidine in the treatment of ventricular arrhythmias. *J Am Coll Cardiol* 1986;7:9-16.
3. Data on file, Bristol Laboratories.

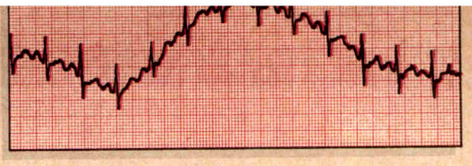
BRISTOL LABORATORIES
Bristol-Myers U.S. Pharmaceutical and Nutritional Group
Evansville, Indiana 47721 U.S.A.
Made in U.S.A. #B-V-20 Revised June, 1987

preparation system Quik-Prep™ because it makes prepping the patient faster. But one look at the traces on the right will tell you we could have named it Stable Baseline Prep. Both traces were from the same patient, the same day, with the same equipment.

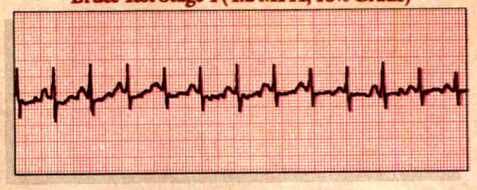
Consistently better ECG traces.

Proper skin preparation is the key to stable baselines. And Quik-Prep is the key to proper skin preparation.

Quik-Prep's patented applicator rotates the center of a special pre-gelled silver-silver chloride electrode. By measuring the electrical impedance of the skin electrode combination, it literally senses when the skin is properly prepared so you get stable ECG baselines, test after test.



Unprepped skin,
Bruce Test Stage 4 (4.2 MPH, 16% Grade)



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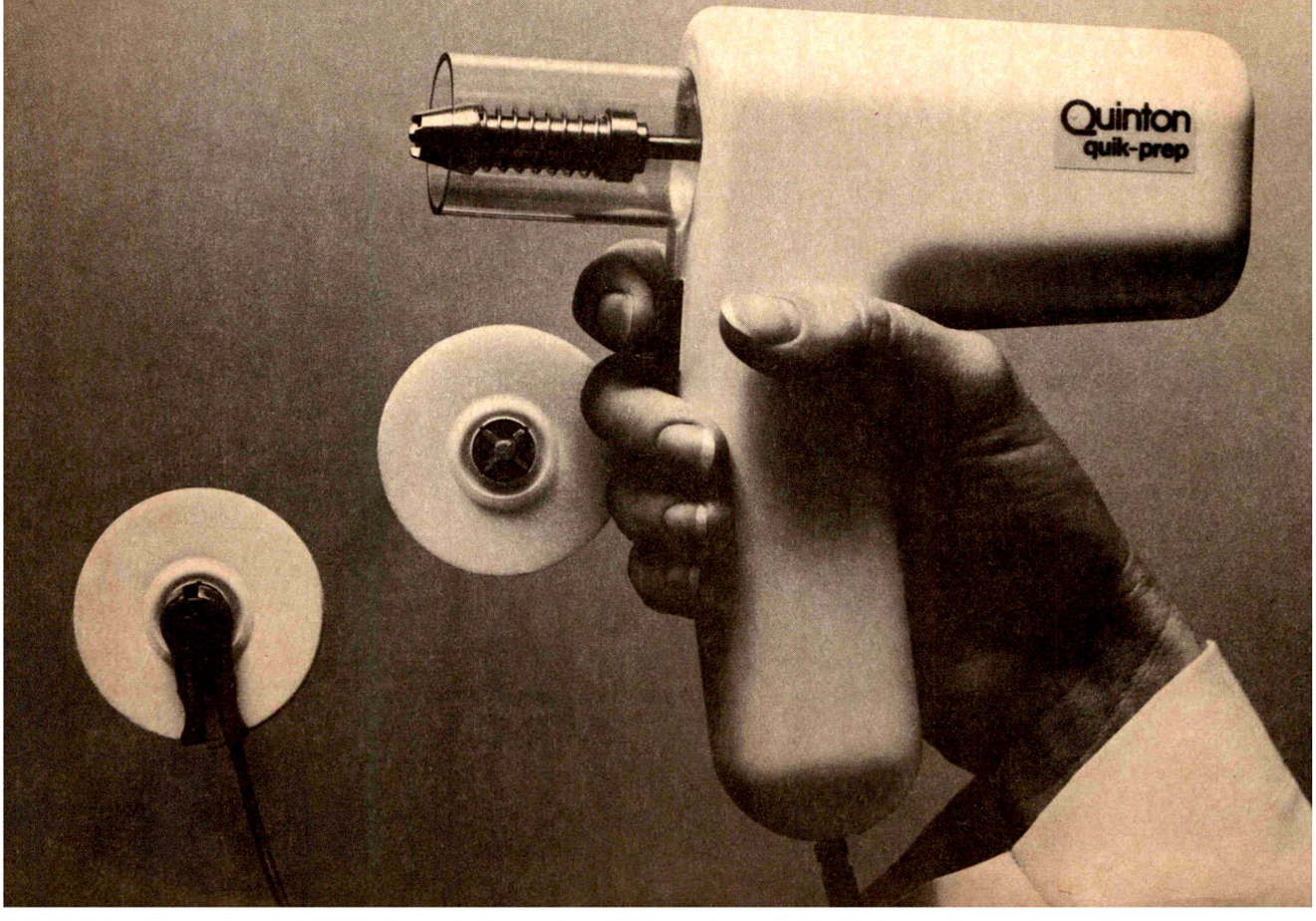
WE COULD HAVE CALLED IT "STABLE BASELINE PREP."



First-step protection for the hypertensive heart

Lopressor®
metoprolol tartrate USP

Tablets
Ampuls
Prefilled Syringes

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.
In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.
Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.
Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.
Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.
Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.
During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.
Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.
AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.
If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.
Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).
Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.
Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.
All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.
No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.
Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient.
Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.
Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)
Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).
Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.
Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.
Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.
There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.
The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.
Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.
Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.
Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.
Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.
Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.
Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.
Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death.
Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.
Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.
Treatment
There is no specific antidote.
In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).
On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:
Elimination of the Drug: Gastric lavage should be performed.
Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.
Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.
Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.
Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

Geigy
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Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

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24-hour security for the hypertensive heart

First-step cardiovascular protection

Reduces workload of the heart by reducing myocardial O_2 demand

Preserves K^+ balance

Normalizes stress-induced systolic peaks with cardioselective beta-one blockade

Contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

Please consult Brief Summary of Prescribing Information on the following page.

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SUSTAINED RELEASE

Before prescribing, please see full prescribing information.
A Brief Summary follows.

> The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

INDICATIONS AND USAGE: Oral procainamide is indicated in the treatment of premature ventricular contractions, ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS: Hypersensitivity to procainamide is an absolute contraindication. In this connection, cross-sensitivity to procaine and related drugs must be borne in mind.

Procainamide should not be administered to patients with complete atrioventricular heart block. It is also contraindicated in cases of second degree and third degree A-V nodal block unless an electrical pacemaker is operative.

It has been suggested that procainamide be contraindicated in patients with myasthenia gravis.

WARNINGS: Granulocytopenia may follow the use of procainamide, and deaths from sepsis have occurred. Leukocyte changes are most likely to occur during the first three months of therapy. During this time routine blood counts should be done at least every two weeks and thereafter at longer intervals throughout maintenance procainamide therapy. Complaints of malaise and aches (a flu-type syndrome) are often reported in association with the granulocyte depression.

Patients should be instructed to report such symptoms promptly, as well as any soreness of mouth, throat or gums, unexplained fever, or symptoms of an upper respiratory tract infection. If these should occur and a complete blood count indicates a granulocyte depression, procainamide therapy should be discontinued immediately and appropriate treatment instituted. Recovery of leukocyte count usually occurs within a few weeks.

The incidence of granulocytopenia appears to be higher with procainamide sustained-release tablets than with standard tablets.

PRECAUTIONS: General — During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgment of mural thrombi and produce an embolic episode. However, it has been suggested that, in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient reevaluated since asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney disease, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Serious hypotension can result from peripheral vasodilation and from decreases in cardiac output. At high plasma levels, procainamide may produce sinus tachycardia due to reflex sympathetic response to its hypotensive effect. Large doses may increase cardiac automaticity and can induce complete atrioventricular block, cardiac standstill, or ventricular extrasystoles that may proceed to ventricular fibrillation. These effects on the myocardium are reflected in the electrocardiogram: a widening of the QRS complex occurs most consistently; less regularly, the P-R and Q-T intervals are prolonged; and the QRS and T waves show some decrease in voltage.

Antinuclear antibodies (ANA) are often found in patients receiving long-term procainamide therapy. The induction of ANA appears to be independent of dosage. Patients with procainamide-induced increases in ANA titers may develop a syndrome resembling systemic lupus erythematosus (SLE). The mechanism of this syndrome is uncertain. Polyarthralgia, arthritic symptoms, and pleuritic pain are common symptoms; to a lesser extent fever, myalgia, skin lesions, pleural effusion, pericarditis, headache, fatigue, weakness, nausea and abdominal pain may occur. Rare cases of thrombocytopenia, Coombs' positive hemolytic anemia, increased SGOT, SGPT, and serum amylase have been reported which may be related to this SLE-like syndrome.

It is recommended that tests for systemic lupus erythematosus be carried out at regular intervals in patients receiving maintenance or prolonged procainamide therapy. The drug should be discontinued if there is a rising ANA titer or clinical symptoms of SLE appear. The SLE-like syndrome may be reversible upon discontinuation of the drug. If discontinuation does not cause remission of the symptoms, corticosteroid therapy may be effective. If the SLE-like syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, corticosteroid suppressive therapy may be used concomitantly with procainamide.

Information for Patient — Practitioners should give the following information and instructions to patients receiving Procan SR. 1. Do not crush or chew these tablets. Swallow them whole. 2. Take this medicine exactly as directed by your doctor. Do not miss any doses and do not take more medicine than ordered. Do not stop taking this medicine without first checking with your doctor. 3. If you miss a dose and remember within one hour or so, take it as soon as possible. Then go back to your regular dosing schedule. Do not take double doses. If you have any questions about this, check with your doctor. 4. Report to your doctor any flu-type symptoms, such as malaise and aches, as well as any soreness of the mouth, throat or gums, unexplained fever, skin rash, unusual bleeding or bruising, symptoms that resemble arthritis, or symptoms of an upper respiratory tract infection. 5. Do not be concerned if you occasionally notice in your stool something that looks like a tablet. In Procan SR (procainamide hydrochloride tablets), the drug is "held" in a wax core that has been specially designed to slowly release the drug for your body to absorb. When this process is completed the empty, nonabsorbable wax core, which looks nearly unchanged, is eliminated from your body. 6. Keep container tightly closed and store in a cool, dry place.

Laboratory Tests — Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals.

Routine blood counts are advisable during maintenance procainamide therapy. See WARNINGS for additional information.

Plasma concentrations of procainamide and NAPA should be monitored in patients with renal disease, hepatic disease, cardiac failure, or low cardiac output states.

Drug Interactions: 1. **Antiarrhythmics:** Concurrent use with procainamide may result in additive cardiac effects and/or additive toxic effects. 2. **Anticholinergics:** Procainamide enhances the anticholinergic effects. Extreme caution must be exercised with such a combination. 3. **Anticholinesterases:** Procainamide antagonizes the effect of anticholinesterases in myasthenia gravis, and paralysis returns. 4. **Antihypertensives:** Procainamide may potentiate the hypotensive effects of thiazide diuretics and other antihypertensive agents. Adjustment of dosage may be required. 5. **Histamine H_2-receptor antagonists:** It has been reported that histamine H_2-receptor antagonists such as cimetidine and ranitidine reduce renal clearance of procainamide and NAPA, resulting in higher plasma concentrations for longer durations. Caution should be exercised when administering these drugs concurrently, especially in the elderly, who have a reduced ability to clear all three. Dosage modification may be required. 6. **Neuromuscular Blocking Agents:** Procainamide potentiates the effects of skeletal muscle relaxants such as succinylcholine. It also may enhance or prolong the neuromuscular blocking activity of bacitracin, colistimethate, dihydrostreptomycin, gentamicin, gramicidin, kanamycin, neomycin, polymyxin B, streptomycin, and viomycin, producing respiratory depression.

Pregnancy — Pregnancy Category C. Animal reproduction studies have not been conducted with procainamide. It is also not known whether procainamide can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Procainamide should be given to a pregnant woman only if clearly needed.

Nursing Mothers — Procainamide and its major metabolite, NAPA, have been identified in breast milk. Caution should be exercised when procainamide is administered to a nursing woman.

ADVERSE REACTIONS: Most frequent, especially with large oral doses: 1. Anorexia; 2. Nausea; 3. Vomiting; 4. Diarrhea; 5. Urticaria; 6. Pruritus.

Less frequent: 1. Reactions in patients on long-term procainamide therapy: a. Antinuclear antibodies (ANA); b. Syndrome resembling systemic lupus erythematosus (SLE) (See PRECAUTIONS); 2. Hypersensitivity reactions: a. Angioneurotic edema; b. Maculopapular rash; c. Fever; d. Eosinophilia; e. Hypergammaglobulinemia.

Infrequent: 1. Granulocytopenia, sometimes resulting in death (See WARNINGS); 2. Convulsions; 3. Psychosis with hallucinations; 4. Confusion; 5. Mental depression; 6. Giddiness; 7. Lightheadedness; 8. Weakness; 9. Bitter taste.

Rare: 1. Hypotension; 2. A case was reported with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following a single dose of the drug.

OVERDOSAGE: Signs and Symptoms: Severe hypotension, ventricular fibrillation, widening of QRS complex, junctional tachycardia, intraventricular conduction delay, oliguria, lethargy, confusion, nausea, and vomiting.

Treatment: If ingestion is recent, emesis, activated charcoal, or gastric lavage may reduce absorption. Dopamine, phenylephrine, or levarterenol may be helpful in reversing severe hypotensive responses.

Management of overdosage includes symptomatic treatment with ECG and blood pressure monitoring. Procainamide toxicity can usually be treated, if necessary, by administering vasopressors after adequate fluid volume replacement. Intravenous infusion of 1/6 molar sodium lactate injection reportedly reduces the cardiotoxic effects of procainamide.

If procainamide toxicity causes severe hypotension and renal insufficiency, urinary elimination of procainamide and NAPA is decreased, and hemodialysis may be required. Hemodialysis significantly reduces the serum half-life of procainamide, and effectively removes procainamide and NAPA. Peritoneal dialysis is not effective.

It has been reported that one patient who ingested approximately 7 grams of procainamide hydrochloride recovered after treatment consisting of IV levarterenol, IV furosemide, attempted volume expansion with albumin, and hemodialysis. Also reported is the case of an elderly patient who recovered after ingestion of approximately 19 grams of procainamide hydrochloride. The patient was treated with IV isoproterenol and IV epinephrine. The latter report suggested that insertion of a ventricular pacing electrode is a reasonable precautionary measure in case high grade A-V block develops.

Storage Conditions: Protect from moisture. Store bottles below 30°C (86°F). Store unit-dose packages at controlled room temperature, 15°-30°C (59°-86°F).

Caution — Federal law prohibits dispensing without prescription. 0207G014

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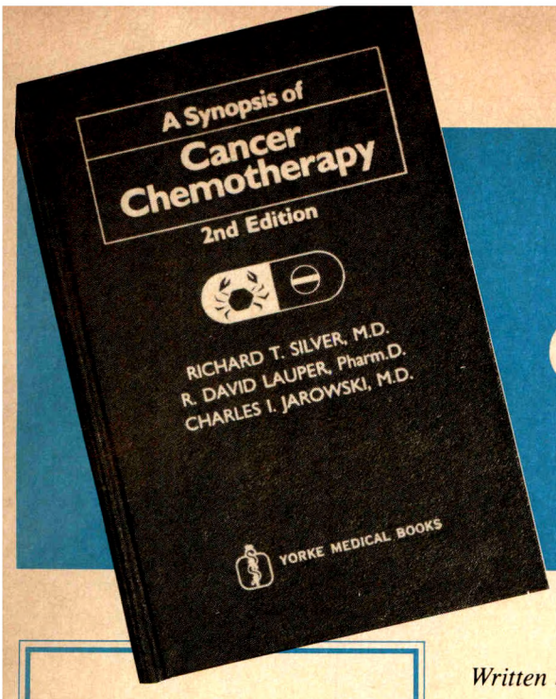

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Precautions: *General.* Severe hypotensive response, particularly with upright posture, may occur even with small doses; therefore use caution in subjects with blood volume depletion from diuretic therapy or with low systolic blood pressure (eg, below 90 mm Hg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrates may aggravate angina caused by hypertrophic cardiomyopathy. Tolerance to this drug and cross-tolerance to other nitrates and nitrites and physical dependence may occur. Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination; dose adjustment of either class of agents may be necessary. There are reports of anginal attacks being more easily provoked and of rebound in hemodynamic effects soon after nitrate withdrawal; when therapy is being terminated, withdraw the drug gradually rather than stopping it abruptly.

Information for Patients. Headache may occur during initial therapy, is usually relieved by standard headache remedies or by lowering dose, and tends to disappear after first week or two.

Drug Interactions. Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates. Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect, depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No long-term studies in animals have been performed.

Pregnancy Category C. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women.

Nursing Mothers. It is not known whether this drug is excreted in human milk; because many drugs are excreted in human milk, caution should be exercised in nursing women.

Pediatric Use. Safety and effectiveness in children have not been established.

Adverse Reactions, particularly headache and hypotension, are dose related. At various doses, the following have been observed: Headache is the most common (average occurrence about 25%) and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to hypotensive effects of nitrates; severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear uncommon.

Overdosage: *Treatment.* Prompt removal of the ingested material by gastric lavage is reasonable but not documented to be useful. Keep the patient recumbent in a shock position and comfortably warm. Passive movements of the extremities may aid venous return. Administer oxygen and artificial respiration if necessary. Conventional doses of organic nitrates could produce harmful concentrations of methemoglobin. If methemoglobinemia is present, administer methylene blue (1% solution), 1 to 2 mg/kg intravenously. WARNING: Epinephrine is ineffective in reversing the severe hypotensive events associated with overdose. It and related compounds are contraindicated in this situation.

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ADD CAPTEN® SOONER*...

(captopril tablets)

SQUIBB

COMPLETE THE JOB YOUR LOOP DIURETIC STARTED

In patients symptomatic on diuretic and digitalis

- ☐ Adding CAPOTEN enhances the diuretic effect of furosemide
  - —Disappearance of edema in 55% of a subgroup of patients after adding CAPOTEN to furosemide†[1]
- ☐ Adding CAPOTEN improves exercise tolerance times in mild, moderate, and severe heart failure patients[2]

IN MILD, MODERATE, AND SEVERE HEART FAILURE (NYHA Class II, III, and IV)

CAPOTEN®

(captopril tablets)

CLOSING THE LOOP IN HEART FAILURE THERAPY

*CAPOTEN is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. See INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS in the brief summary of prescribing information on adjacent page.

†Patients for whom data were available for two months. Patients were NYHA Class II, III, or IV receiving concomitant diuretic and digitalis therapy.

CLOSING THE LOOP IN HEART FAILURE THERAPY

SQUIBB

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $<1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* – Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* – If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension – Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

References:

1. The Captopril Multicenter Research Group I: A cooperative multicenter study of captopril in congestive heart failure: Hemodynamic effects and long-term response. Am Heart J 110: 439-447, 1985.
2. Captopril Multicenter Research Group: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Coll Cardiol 2:755-763, 1983.

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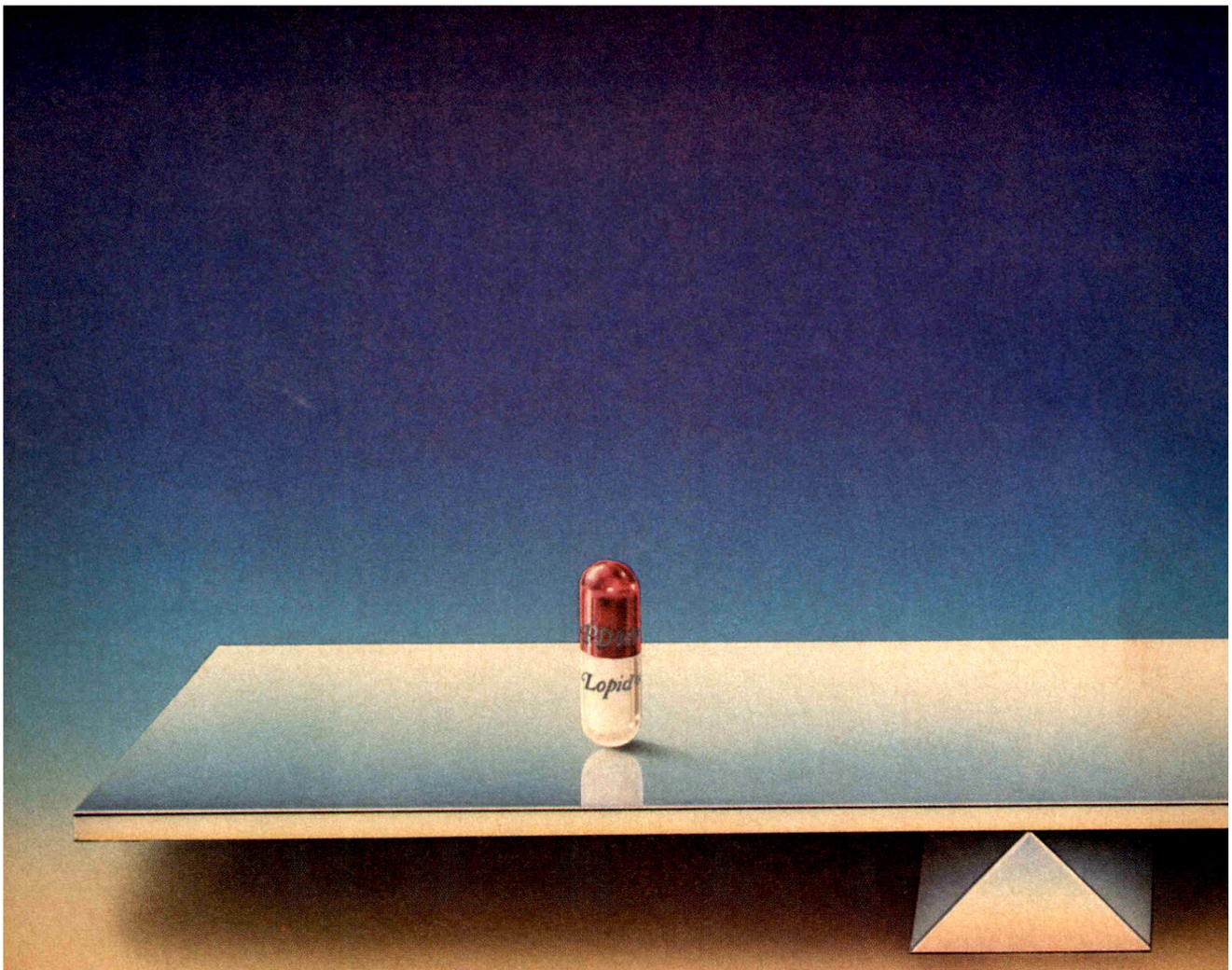

IN CERTAIN DYSLIPIDEMIAS

A Desirable Balance of Efficac

LOPID® *300 mg*
(gemfibrozil capsules, USP)

Lopid is indicated for treatment of adult patients with very high serum triglyceride levels in hyperlipoproteinem other than type I who present a risk of pancreatitis and who do not respond adequately to diet.

© 1987 Warner-Lambert Company

with Patient Acceptance

Efficacy Lopid reduces synthesis[1-3] and increases clearance of triglyceride-rich VLDL.[2,3]

Patient acceptance Lopid has a very low order of side effects and has demonstrated limited effects on clinical and laboratory evaluations.[4]

Convenient BID dosage Two 300-mg capsules taken 30 minutes before morning and evening meals help ensure patient compliance.

Diet, exercise, and weight loss are the first choice in therapy of lipid disorders.

PARKE-DAVIS

Please see next page for references and a brief summary of prescribing information.

LOPID®
(gemfibrozil capsules, USP) 300 mg

Before prescribing, please see full prescribing information. A Brief Summary follows:

CLINICAL PHARMACOLOGY. LOPID is a lipid regulating agent which lowers elevated serum lipids primarily by decreasing serum triglyceride with a variable reduction in total serum cholesterol. These decreases occur primarily in the very low density lipoprotein (VLDL) fraction and less frequently in the low density lipoprotein (LDL) fraction. It has been reported that LOPID may increase levels of high density lipoprotein (HDL) subfractions, HDL_2 and HDL_3 as well as apolipoproteins AI and AII. Epidemiological studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease. It is not yet known whether pharmacological interventions designed to raise HDL-cholesterol alter morbidity or mortality due to coronary heart disease.

The mechanism of action has not been definitively established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID inhibits synthesis and increases clearance of VLDL carrier apolipoprotein B, leading to a decrease in VLDL production.

Animal studies suggest that LOPID may, in addition to elevating HDL cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces.

LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in one to two hours with a plasma half-life of 1.5 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, mostly as the glucuronide conjugate, with less than 2% excreted as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

In a large, controlled multicenter trial of 427 patients, lipid and lipoprotein changes from average baseline (%) by hyperlipoproteinemic (HLP) type are summarized below for those patients receiving gemfibrozil, 1200 mg/day, at the end of 12 weeks.

HLP Type	TRIGLYCERIDE	CHOLESTEROL				RATIO: HDL Cholesterol / Total Cholesterol
		Total	VLDL	LDL	HDL	
IIa	−44%	−4.2%	−44.3%	−5.8%	+24.6%	+33%
IIb	−45%	−8.6%	−45.0%	−6.4%	+19.5%	+34%
IV	−40%	−1.8%	−40.8%	+14.6%	+17.4%	+23%

INDICATIONS AND USAGE. The initial treatment for hyperlipidemia is dietary therapy specific for the type of hyperlipoproteinemia. Drug therapy should not be used for the routine treatment of elevated blood lipids for the prevention of coronary heart disease. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Contributory diseases such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, and the adverse findings with clofibrate in two large clinical studies (see Warnings), use of gemfibrozil should be restricted to the following indications.

LOPID may be considered for the treatment of adult patients with very high serum triglyceride levels (type IV or type V hyperlipoproteinemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk. LOPID has little effect on elevated cholesterol levels in most subjects. A minority of subjects show a more pronounced response. Therefore, the physician should be very selective and confine gemfibrozil treatment to patients with clearly defined risk due to severe hypercholesterolemia (eg, individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

LOPID is not useful for the hypertriglyceridemia of Type I hyperlipidemia.

The biochemical response to gemfibrozil is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued after three months in any patient in whom lipids do not show significant improvement.

The effect of gemfibrozil-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL cholesterol levels on morbidity or mortality due to coronary heart disease has not been established. Several years may be required before ongoing long-term investigations will resolve this question.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease. (See Warnings).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization, 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant 36% higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

2. Long-Term Toxicity and Animal Tumorigenicity Studies – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p greater than 0.05). There were no statistically significant differences from controls in the incidence of liver tumors in female rats, and in male and female mice.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID (gemfibrozil capsules, USP) administration to the male rat. Similar changes have not been found in the human liver.

Male rats had a dose-related increase of benign Leydig cell tumors. Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of the high dose males.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and liver and interstitial cell testicular tumors were increased in male rats, LOPID should be administered only to those patients described in the Indications and Usage Section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Cholelithiasis – LOPID may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

5. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

PRECAUTIONS. 1. **Initial Therapy** – Before instituting LOPID therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and other medical problems such as diabetes mellitus and hypothyroidism.

2. **Continued Therapy** – Pretreatment laboratory studies should be performed to ensure that patients have abnormal levels of serum lipids. Periodic determinations of serum lipids should be obtained during LOPID administration. The drug should be withdrawn after three months if the lipid response is inadequate.

3. **Impairment of Fertility** – Administration of approximately three and ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to their offspring.

4. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to LOPID. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that LOPID is tumorigenic in male rats, the use of LOPID in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

5. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in male rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

6. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

7. **Liver Function** – Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of SGOT, SGPT, LDH, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

8. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In controlled clinical trials of 805 patients, including 245 who received LOPID for at least one year, the most frequently reported adverse reactions associated with LOPID involved the gastrointestinal system. In decreasing order of frequency, these were abdominal pain (6.0%), epigastric pain (4.9%), diarrhea (4.8%), nausea (4.0%), vomiting (1.6%), and flatulence (1.1%). Other adverse reactions where the probability of a causal relationship to LOPID therapy exists are listed by system.

Integumentary: rash, dermatitis, pruritus, urticaria

Central Nervous System: headache, dizziness, blurred vision

Musculoskeletal: painful extremities

Hematopoietic: anemia, eosinophilia, leukopenia

Other reactions have been reported under conditions where a causal relationship is difficult to establish, thus the physician should be alert to these occurrences. Reports of viral and bacterial infections (common cold, cough, and urinary tract infections) were more common in gemfibrozil than in placebo-treated patients.

Other reactions were:

Gastrointestinal: dry mouth, constipation, anorexia, gas pain, dyspepsia

Musculoskeletal: back pain, arthralgia, muscle cramps, myalgia, swollen joints, myositis

Central Nervous System: vertigo, insomnia, paresthesia, tinnitus

Clinical Laboratory: hypokalemia, liver function abnormalities (increased SGOT, SGPT, LDH, CPK, alkaline phosphatase)

Miscellaneous: fatigue, malaise, syncope, alopecia

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal. Some patients will experience therapeutic effects on 900 mg/day; a few may require 1500 mg/day for satisfactory results.

DRUG INTERACTIONS. CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

MANAGEMENT OF OVERDOSAGE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

Caution – Federal law prohibits dispensing without prescription.

February 1987 0669G017

REFERENCES 1. Kashyap ML: The effect of gemfibrozil on plasma lipids and lipoproteins in man. *Vasc Med* 1984;1:16-21. 2. Kesäniemi YA, Grundy SM: Influence of gemfibrozil and clofibrate on metabolism of cholesterol and plasma triglycerides in man. *JAMA* 1984;251:2241-2246. 3. Brown MS, Goldstein JL: Drugs used in the treatment of hyperlipoproteinemias, in Gilman AG, Goodman LS, Rall TW, et al (eds): *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co, 1985, pp 827-845. 4. Lewis JE and the Multicenter Collaborative Study Group: Clinical use of gemfibrozil: A controlled multicenter trial. *Pract Cardiol* 1983;9(6):99-118.

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MISCELLANEOUS TOPICS

875 **Left Ventricular Dysfunction After Prolonged Strenuous Exercise in Healthy Subjects**

Douglas R. Seals, Marc A. Rogers, James M. Hagberg, Chikashi Yamamoto, Philip E. Cryer, and Ali A. Ehsani

To examine whether left ventricular dysfunction can occur following prolonged strenuous exercise in healthy subjects, 12 young men were studied before and after 170 ± 10 minutes of exercise at an intensity of 70% of their maximal aerobic capacity. Ejection phase indexes of left ventricular function, assessed by echocardiography, decreased after exhausting exercise despite a lower end-systolic wall stress. Plasma free fatty acids increased after exhausting exercise. The data suggest that exhausting exercise can result in impaired left ventricular function in healthy young subjects.

880 **The 24-Hour Heart Rate Behavior in Long-Term Survivors of Cardiac Transplantation**

Dimitrios Alexopoulos, Salim Yusuf, Jim A. Johnston, Julian Bostock, Peter Sleight, and Magdi H. Yacoub

Ambulatory monitoring of heart rate (HR) was performed in 19 long-term survivors of cardiac transplantation (12 orthotopic, 7 heterotopic) and in 10 normal volunteers. The transplanted denervated and the recipient innervated hearts in the heterotopic group showed higher than normal average HRs over 24 hours, waking and sleeping periods. Maximal HR was similar in the 3 groups, but the minimal HR was lower in normal hearts than in the denervated and recipient hearts. The 24-hour HR variability was reduced in the denervated hearts. During arousal from sleep, HR changes were smaller in the denervated and recipient hearts compared with normal hearts. The denervated heart can show significant HR variations, but to a lesser extent than normal. In heterotopic transplant recipients, the patients' own HR changes also are significantly blunted.

METHODS

885 **Optimal Lead Subsets for Reconstruction of QRS and ST-T in 35-Lead Precordial Maps**

Christopher D. McManus, Alan S. Berson, Jorge C. Rios, Emigdio A. Lopez, and Hubert V. Pipberger

Precordial maps have been used for 15 years to estimate extent of myocardial injury in patients with acute anterior or lateral wall infarction. Application of the electrodes, commonly 35, is cumbersome and time-consum-

ing with the critically ill. A subset of only 5 or 7 selected leads can be applied instead, and the remaining leads calculated from the subset with minimal loss of QRS and ST-T information. Maps were recorded from 100 patients within 72 hours of onset of infarct. Optimal subsets numbering between 2 and 15 leads were derived, with their lead-transform coefficients, by the sequential selection method of Lux. Reconstruction from a 7-lead subset had a mean 0.92 correlation with ST-T in the original leads and root-mean-square error of only 0.04 mV. Sum of ST elevation differed by only 2% between original leads and reconstructions based on 5 or more leads.

891 Limits of Reproducibility of Mitral Pulsed Doppler Spectra

Jules Fast, Ina Van Dam, Anco Heringa, Theo De Boo, Jos Alsters, Jeroen Hopman, Otto Daniels, and Lambert Van Den Merkhof

In this study we evaluated the total intrinsic variability of pulsed Doppler spectra of mitral blood flow. Doppler examinations were performed in 10 normal volunteers (7 men, 3 women), ages 29 to 57 years with an interval period of 3 months. The recordings were made in the apical 4-chamber view. The sample was placed approximately 1 cm proximal (left atrium) and 1 cm distal (left ventricle) of the middle of the anulus of the mitral valve at the onset of diastole. Mitral peak velocities, accelerations and spectral widths were measured in early diastole and late diastole. From the parameters under investigation, maximal velocities showed the best reproducibility with a range of coefficients of variation of 9 to 13%. Peak acceleration in early diastole and spectral widths showed rather large coefficients of variation, ranging from 19 to 30 and 14 to 24%, respectively. Mitral pulsed Doppler spectra in the left atrium were more reproducible than in the left ventricle.

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895 From Irritable Heart to Mitral Valve Prolapse: World War I—The U.S. Experience and the Prevalence of Apical Systolic Murmurs and Mitral Regurgitation in Drafted Men Compared with Present Day Mitral Valve Prolapse Studies

Charles F. Wooley and Harisios Boudoulas

900 Lewis A. Conner, MD (1867–1950), and Lessons Learned from Examining Four Million Young Men in World War I

Charles F. Wooley

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Freek W.A. Verheugt, Albert J. Funke Küpper, Tjebbe W. Galema, and Jan P. Roos

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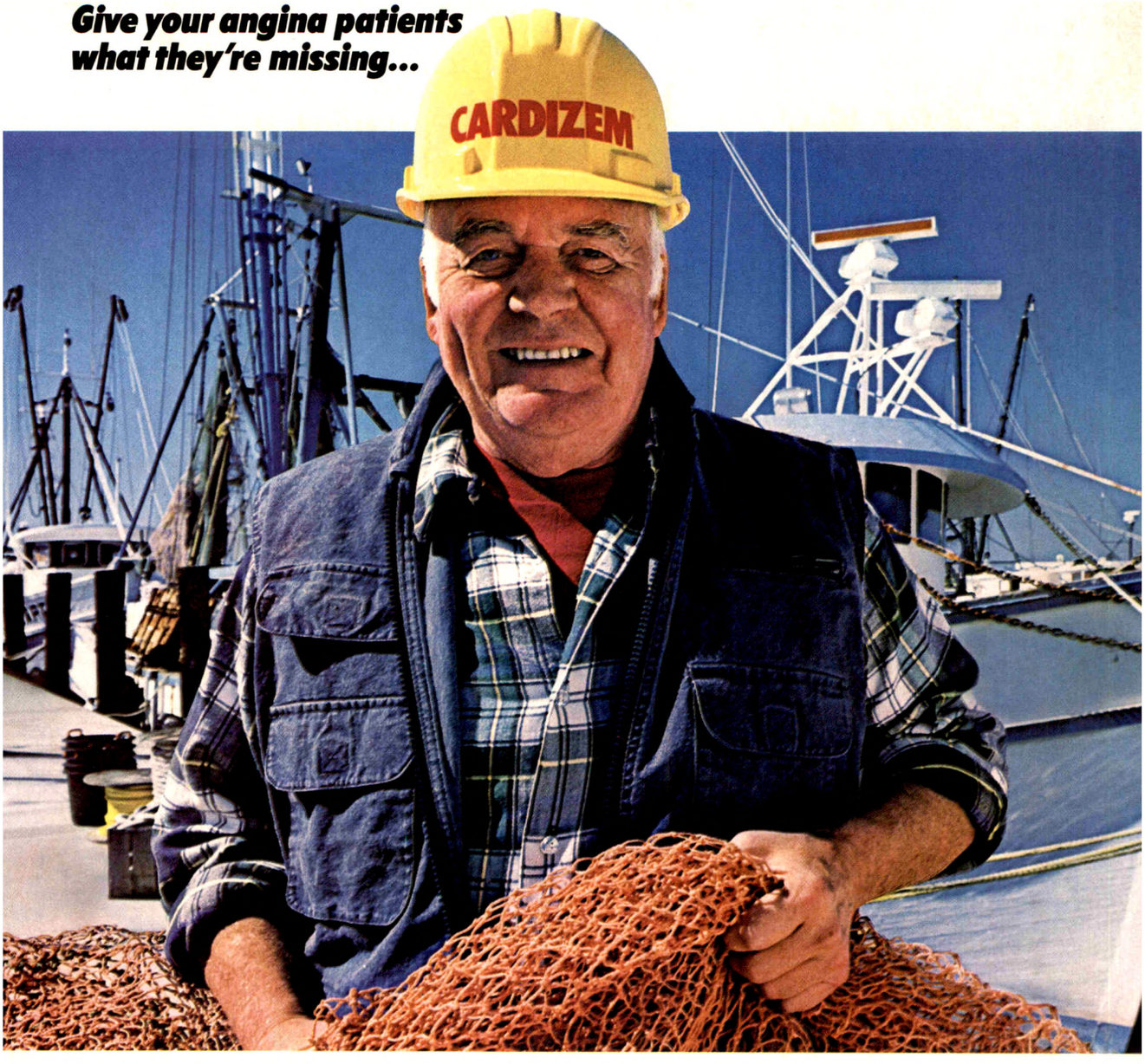

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CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), and (4) patients who have demonstrated hypersensitivity to the drug.

WARNINGS

1. ***Cardiac Conduction.*** *CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.*
2. ***Congestive Heart Failure.*** *Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.*
3. ***Hypotension.*** *Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.*
4. ***Acute Hepatic Injury.*** *In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)*

PRECAUTIONS

General. *CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.*

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. *Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)*

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: *Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.*

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: *A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.*

Digitalis: *Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)*

Carcinogenesis, Mutagenesis, Impairment of Fertility. *A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.*

Pregnancy. *Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/ postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.*

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. *Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.*

Pediatric Use. *Safety and effectiveness in children have not been established.*

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	*Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope.*
Nervous System:	*Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.*
Gastrointestinal:	*Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.*
Dermatologic:	*Petechiae, pruritus, photosensitivity, urticaria.*
Other:	*Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.*

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established. *Issued 6/87*

See complete Professional Use Information before prescribing.

References: ***1.*** *Pepine CJ, Feldman RL, Hill JA, et al: Clinical outcome after treatment of rest angina with calcium blockers: Comparative experience during the initial year of therapy with diltiazem, nifedipine, and verapamil. Am Heart J 1983; 106(6):1341-1347.* ***2.*** *Shapiro W: Calcium channel blockers: Actions on the heart and uses in ischemic heart disease. Consultant 1984;24(Dec):150-159.* ***3.*** *Johnston DL, Lesoway R, Humen DP, et al: Clinical and hemodynamic evaluation of propranolol in combination with verapamil, nifedipine and diltiazem in exertional angina pectoris: A placebo-controlled, double-blind, randomized, crossover study. Am J Cardiol 1985;55:680-687.* ***4.*** *Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39.* ***5.*** *Schroeder JS: Calcium and beta blockers in ischemic heart disease: When to use which. Mod Med 1982;50(Sept):94-116.*

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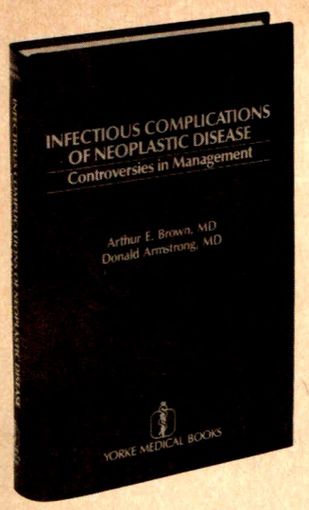

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The result is a concise, dynamic study that belongs in the professional library of every physician treating patients with neoplastic disease.

About the Editors

Arthur E. Brown, MD, is Assistant Attending Physician, Memorial Sloan-Kettering Cancer Center, and Assistant Professor of Medicine and Pediatrics, Cornell University Medical College.

Donald Armstrong, MD, is Attending Physician; Chief of Service; Director, Microbiology Laboratory, Memorial Sloan-Kettering Cancer Center, and Professor of Medicine, Cornell University Medical College

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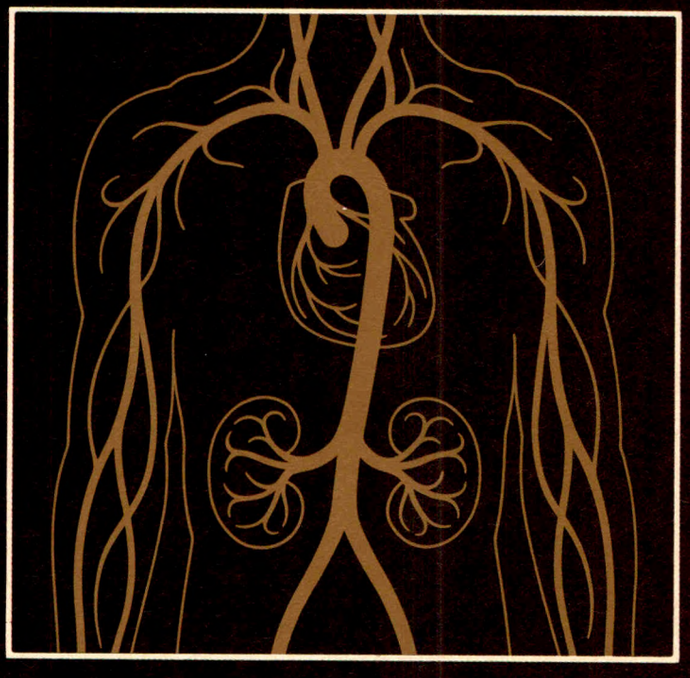

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BRIEF SUMMARY

Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure<90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present).

Warnings: Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction<30%) or moderate to severe symptoms of cardiac failure and in patients with significant ventricular dysfunction if they are receiving a beta-adrenergic blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce a decrease in blood pressure below normal levels, which may result in dizziness or symptomatic hypotension. Elevations of liver enzymes have been reported. Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). The effect of verapamil on AV conduction and the SA node may cause asymptomatic 1st-degree AV block and transient bradycardia, sometimes with nodal escape rhythms. PR-interval prolongation is correlated with verapamil plasma concentrations especially during initial titration. Higher degrees of AV block are infrequent (0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Studies in a small number of patients suggest that concomitant use of Calan and oral beta-adrenergic blockers may be beneficial in certain patients with chronic stable angina or hypertension. Combined therapy can also have adverse effects on cardiac function; therefore patients should be closely monitored. A decrease in metoprolol clearance may occur with concurrent use of verapamil and metoprolol. Chronic verapamil treatment increases serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient reassessed. Verapamil used concomitantly with oral antihypertensive agents will usually have an additive effect on lowering blood pressure that in some cases may be excessive; therefore patients should be monitored appropriately. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Quinidine levels may increase during verapamil therapy. Clearance of verapamil may be reduced in concomitant use with cimetidine. Concomitant use of verapamil and lithium may result in decreased serum lithium levels. Verapamil therapy may increase carbamazepine concentrations during combined use. Therapy with rifampin may markedly reduce oral verapamil bioavailability. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Another study in rats showed no evidence of carcinogenicity. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy in children under 18 have not been established.

Adverse Reactions— oral verapamil: Constipation (8.4%), dizziness (3.5%), nausea (2.7%), hypotension (2.5%), edema (2.1%), headache (1.9%), CHF/pulmonary edema (1.8%), fatigue (1.7%), bradycardia: HR <50/min (1.4%), AV block: total 1°, 2°, 3° (1.3%)/3rd-degree (0.8%), flushing (0.1%); elevations of liver enzymes have been reported (see *Warnings*). The following reactions, reported in 1.0% or less of patients, occurred under circumstances where a causal relationship is not certain: angina pectoris, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, dyspnea, arthralgia, rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, blurred vision, gynecomastia, impotence, increased urination, spotty menstruation.

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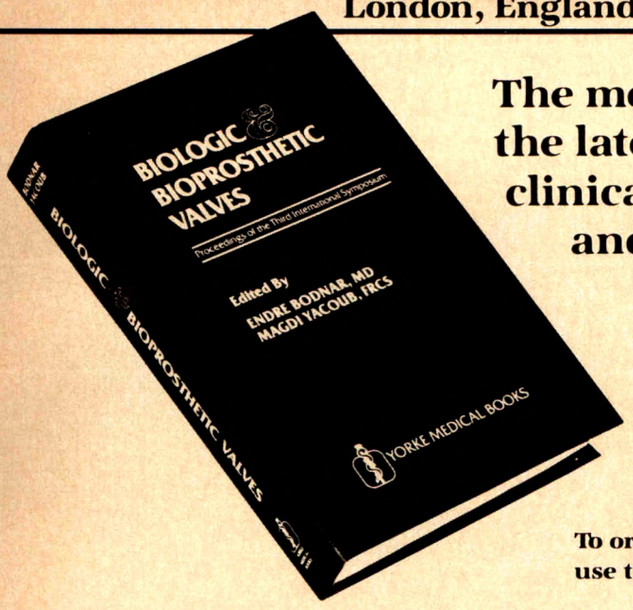

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The Third International Symposium on Cardiac Bioprostheses was held May 21-23, 1985, at the Grosvenor House Hotel, London. Six years have passed since the first meeting of this kind was held in Munich and 3 years since the second conference in Rome. The reassessment of the state of the art with biologic and bioprosthetic valves seems to have become a regular 3-yearly fixture reflecting the fast development of these devices, as well as the desire of surgeons and academics working in this field to share experiences, exchange ideas, and to resolve problems together.

The London meeting brought together surgeons, cardiologists, pathologists, engineers, and basic scientists, and the 3-day program accommodated 96 formal presentations with nearly 7 hours of discussion. It is a credit to the session chairmen and participants that the discussions were frank, outspoken, but fair and always to the point, and they have been added to this volume, and they certainly enhance its value.

This volume incorporates the work of the best specialists in the field, and should not be missing from your own professional library.

The Editors are eminently qualified to do this book, Dr. Bodnar is with the Cardiothoracic Institute, London, England, and Mr. Yacoub is with Harefield Hospital, Middlesex, England.

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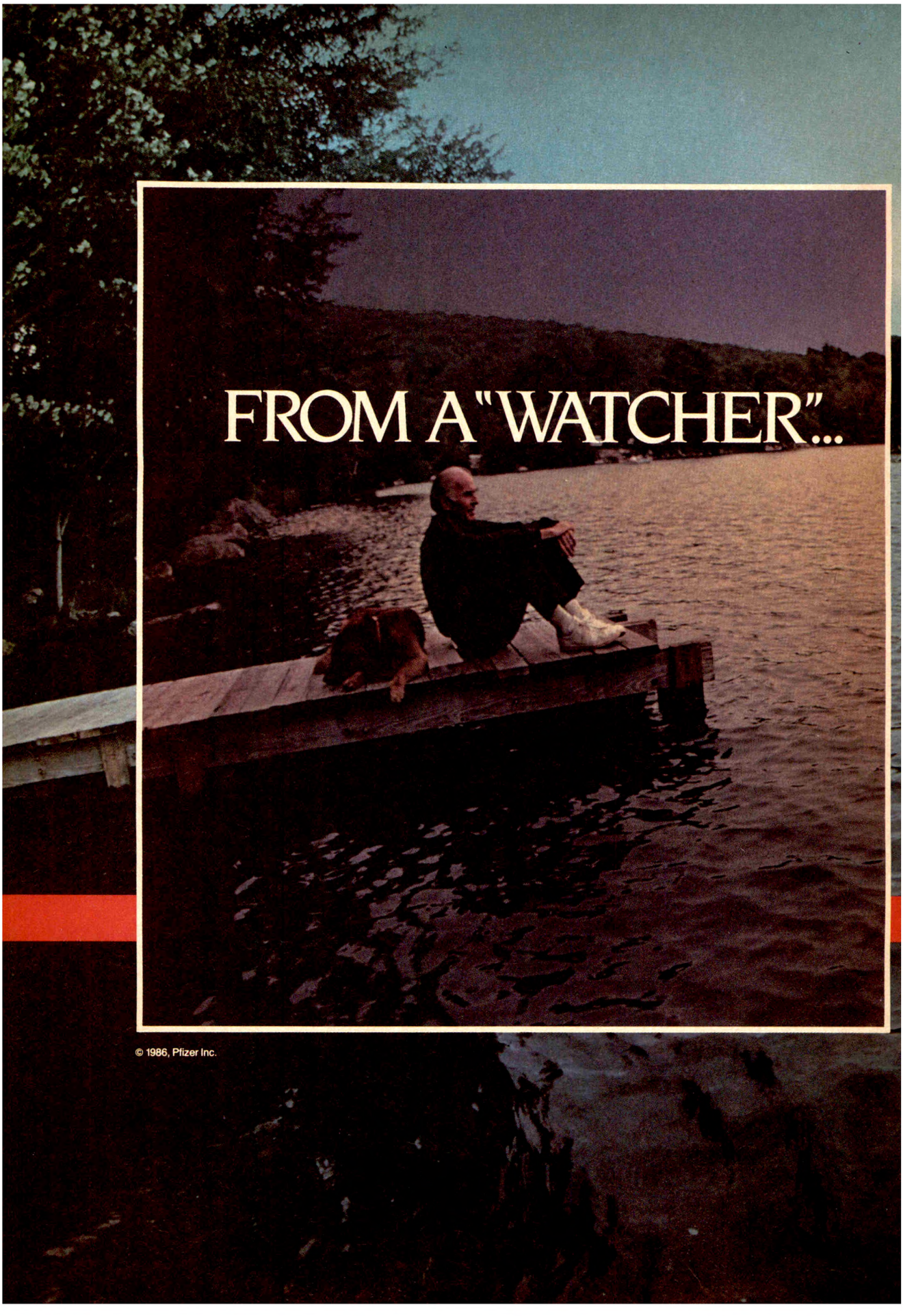

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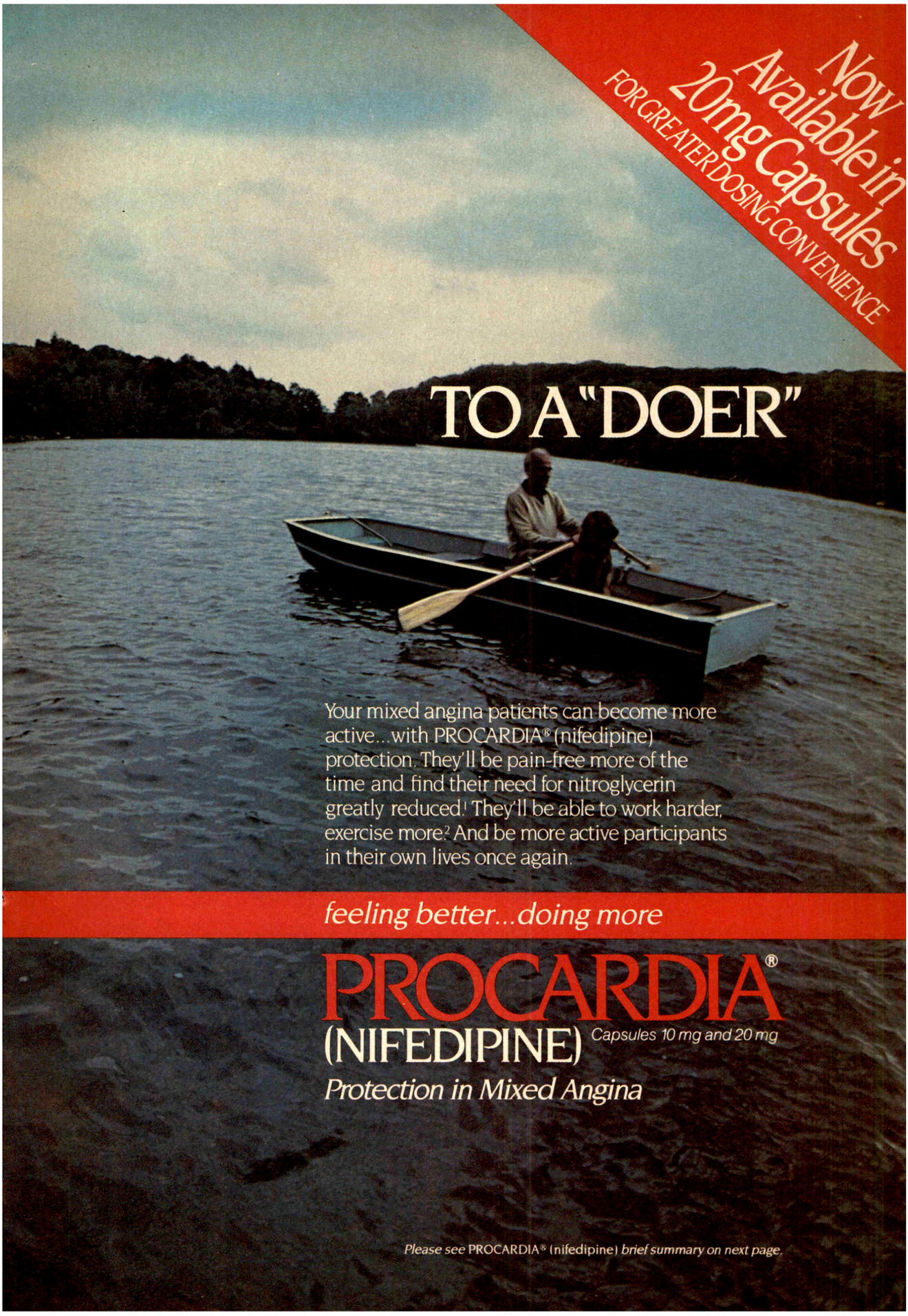
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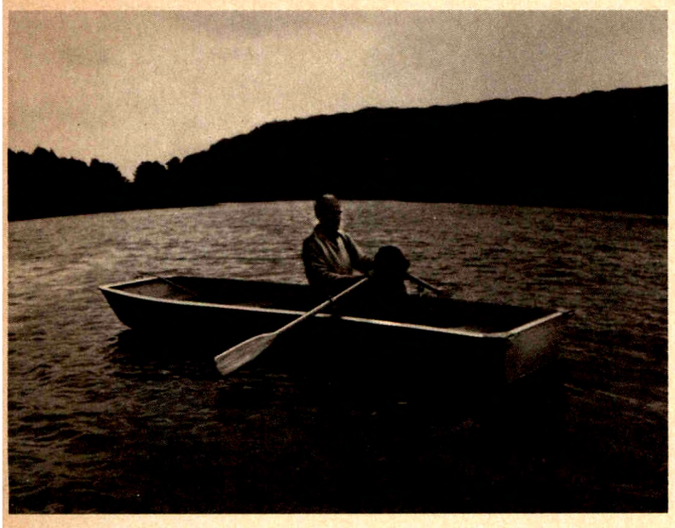

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Because PROCARDIA decreases peripheral vascular resistance (occasional patients have had excessive hypotension), careful monitoring of blood pressure during initial administration and upward dosage titration is suggested, especially for patients taking other drugs known to lower blood pressure. Occasional patients have developed increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases.

–Offers a favorable safety profile

Most frequently reported side effects associated with PROCARDIA therapy, usually mild, are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients; transient hypotension in about 5%; palpitation in about 2%; syncope in about 0.5%.

References:

1. Stone PH, Muller JE, Turi ZG, et al: Efficacy of nifedipine therapy in patients with refractory angina pectoris: Significance of the presence of coronary vasospasm. *Am Heart J* 1983; 106:644-652.
2. Morse JR, Nesto RW: Double-blind crossover comparison of the antianginal effects of nifedipine and isosorbide dinitrate in patients with exertional angina receiving propranolol. *J Am Coll Cardiol* 1985; 6:1395-1401.

Brief Summary

PROCARDIA® (nifedipine) Capsules For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting PROCARDIA or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Laboratory tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to PROCARDIA therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have been reported.

Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some PROCARDIA (nifedipine) patients. No clinical significance for these findings has been demonstrated. Positive direct Coombs test with/without hemolytic anemia has been reported.

Although PROCARDIA has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare, reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to PROCARDIA therapy is uncertain in most cases but probable in some.

Drug interactions: Beta-adrenergic blocking agents: (See INDICATIONS AND WARNINGS.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Coumarin anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom PROCARDIA was administered.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%) after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats and embryotoxic in rats, mice and rabbits. There are no adequate and well controlled studies in pregnant women. PROCARDIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: The most common adverse events include dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, shortness of breath, diarrhea, constipation, gastrointestinal cramps, flatulence, inflammation, joint stiffness, shakiness, jitteriness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties, thrombocytopenia, anemia, leukopenia, purpura, allergic hepatitis, gingival hyperplasia, depression, paranoid syndrome, transient blindness at the peak of plasma level, erythromelalgia, and arthritis with ANA (+). Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

HOW SUPPLIED: PROCARDIA soft gelatin capsules are supplied in:
Bottles of 100: 10 mg (NDC 0069-2600-66) orange #260; 20 mg (NDC 0069-2610-66) orange and light brown #261. Bottles of 300: 10 mg (NDC 0069-2600-72) orange #260; 20 mg (NDC 0069-2610-72) orange and light brown #261. Unit dose packages of 100: 10 mg (NDC 0069-2600-41) orange #260; 20 mg (NDC 0069-2610-41) orange and light brown #261.

The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request. Revised June 1986 © 1982, Pfizer Inc

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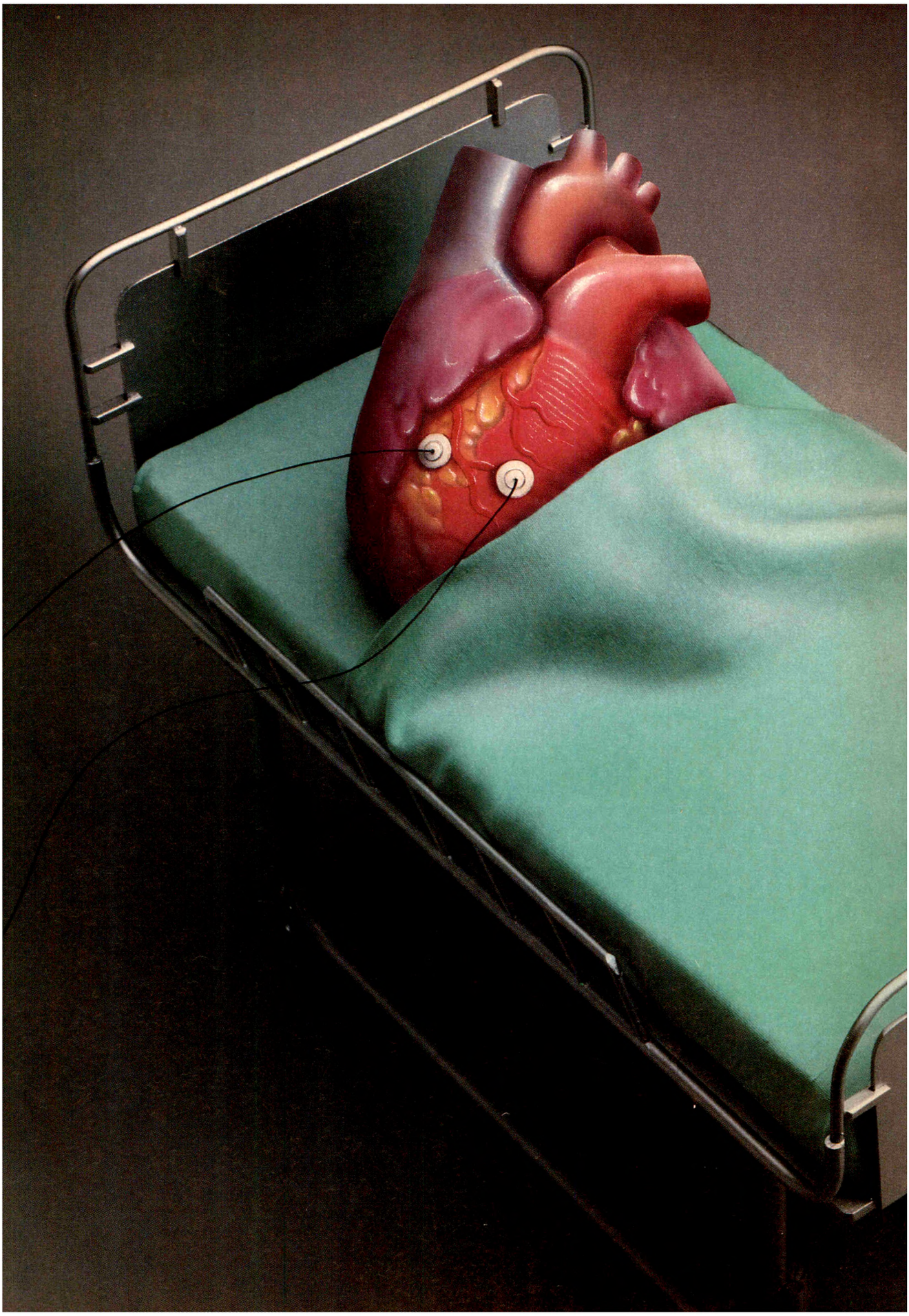

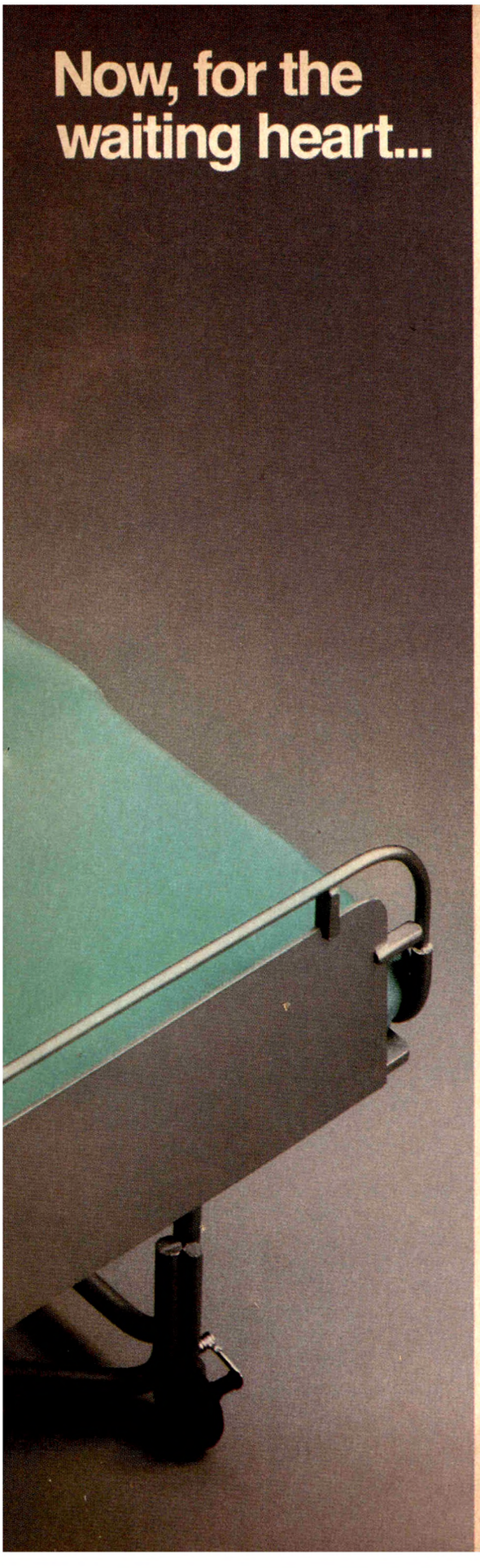

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REFERENCES: 1. Piran U, Kohn DW, Uretsky LS et al: Immunochemiluminometric assay of creatine kinase MB with a monoclonal antibody to the MB isoenzyme. *Clin Chem* 1987;33:1517-1520. 2. Data on file, CIBA–CORNING Diagnostics Corp.

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Vaseretic®

(Enalapril Maleate-Hydrochlorothiazide|MSD)

For added hypertension control

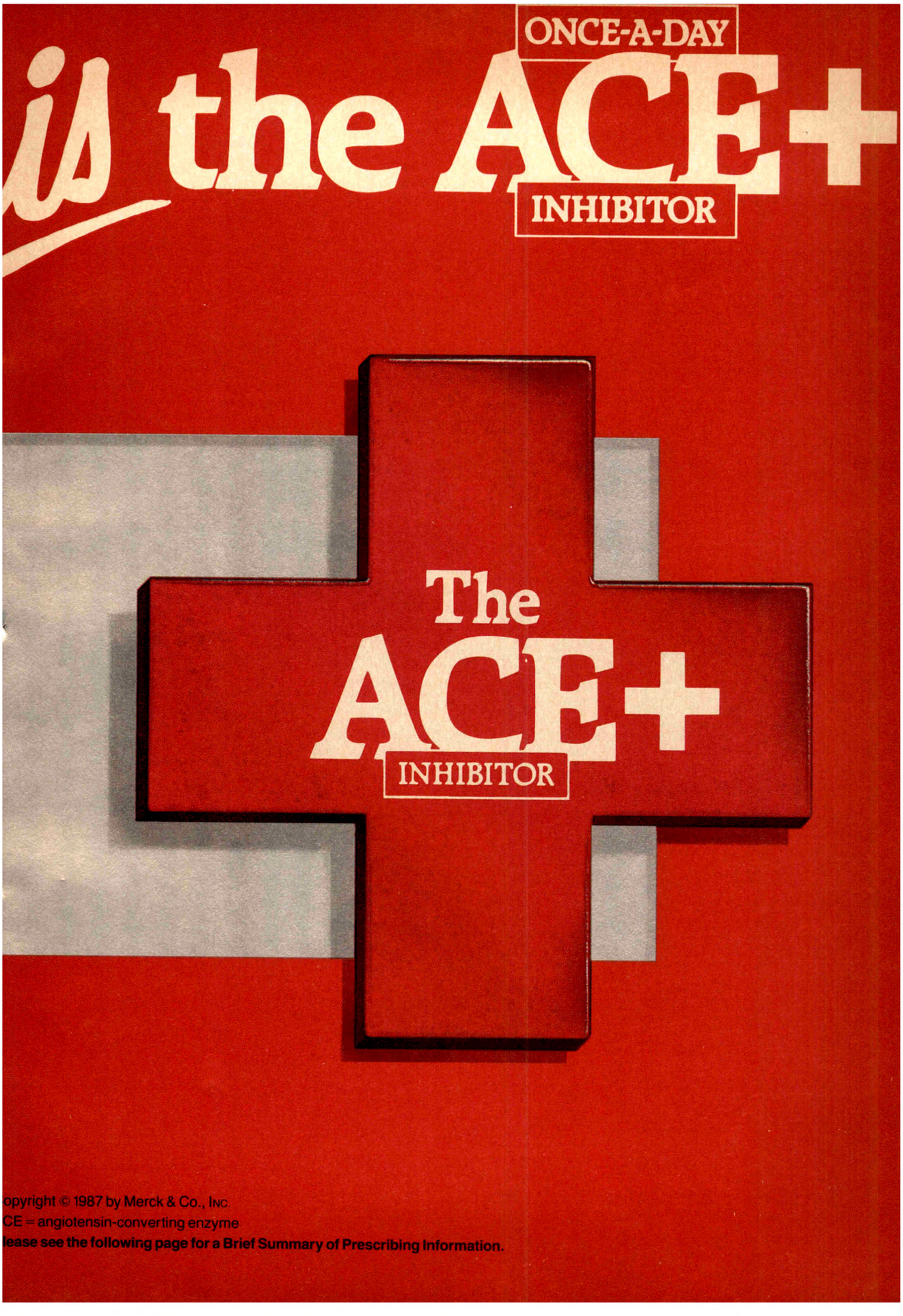
- **Hydrochlorothiazide** augments the antihypertensive effect of enalapril.
- **Enalapril** tends to reverse the potassium loss often associated with hydrochlorothiazide.
- Highly effective in adults, regardless of age or race.*

This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapri at a low initial dose (2.5 mg; see DOSAGE AND ADMINISTRATION). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

VASERETIC, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide, is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Evaluation of the hypertensive patient should always include assessment of renal function.

*Although enalapril was antihypertensive in all races studied, black hypertensive patients (usually a low-renin hypertensive population) had a smaller average response to enalapril maleate monotherapy than non-black patients. In contrast, hydrochlorothiazide was more effective in black patients than enalapril. Concomitant administration of enalapril maleate and hydrochlorothiazide was equally effective in black and non-black patients.



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CE = angiotensin-converting enzyme

lease see the following page for a Brief Summary of Prescribing Information.

Once-A-Day
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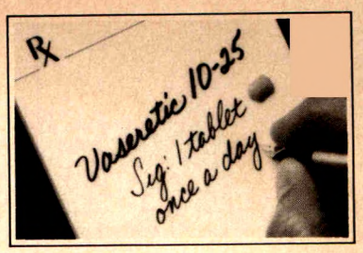

This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated, or given a diuretic and enalapril simultaneously, can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, begin enalapril at a low initial dose (see DOSAGE AND ADMINISTRATION in complete Prescribing Information). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

CONTRAINDICATIONS

VASERETIC® (Enalapril Maleate-Hydrochlorothiazide, MSD) is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

Hypotension: Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. Syncope has been reported in 1.3% of patients receiving VASERETIC. In patients receiving enalapril alone, the incidence of syncope is 0.5%. The overall incidence of syncope may be reduced by proper titration of the individual components (see PRECAUTIONS, Drug Interactions; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION in complete Prescribing Information). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses, which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with angiotensin-converting-enzyme inhibitors, including enalapril. In such cases, VASERETIC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered** (see ADVERSE REACTIONS).

Neutropenia/Agranulocytosis: Another angiotensin-converting-enzyme inhibitor has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions: Hydrochlorothiazide).

PRECAUTIONS

General: ***Enalapril Maleate:*** *Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting-enzyme inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.**

Hyperkalemia: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with enalapril alone. In most cases, these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1%) in patients treated with enalapril plus hydrochlorothiazide. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia (see Drug Interactions).

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: namely hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see Drug Interactions: Agents Increasing Serum Potassium).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Information for Patients: *Angioedema:* Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue and/or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC® (Enalapril Maleate-Hydrochlorothiazide, MSD) is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Enalapril Maleate:*** *Hypotension—Patients on Diuretic Therapy:* Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide medical supervision for at least one hour after the initial dose (see WARNINGS and DOSAGE AND ADMINISTRATION). *Agents Causing Renin Release:* The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics). *Other Cardiovascular Agents:* Enalapril has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions. *Agents Increasing Serum Potassium:* Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Hydrochlorothiazide: When administered concurrently, the following drugs may interact with thiazide diuretics. *Alcohol, barbiturates, or narcotics*—potentiation of orthostatic hypotension may occur. *Antidiabetic drugs (oral agents and insulin)*—dosage adjustment of the antidiabetic drug may be required. *Other antihypertensive drugs*—additive effect or potentiation. *Corticosteroids, ACTH*—intensified electrolyte depletion, particularly hypokalemia. *Pressor amines (e.g., norepinephrine)*—possible decreased response to pressor amines but not sufficient to preclude their use. *Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)*—possible increased responsiveness to the muscle relaxant. *Lithium*—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC. *Nonsteroidal anti-inflammatory drugs*—In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when VASERETIC and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Pregnancy: ***Enalapril Maleate-Hydrochlorothiazide:*** *Pregnancy Category C.* There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2-1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of hydrochlorothiazide (2-1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses: 30/10 mg/kg/day of enalapril-hydrochlorothiazide in rats and 10/10 mg/kg/day of enalapril-hydrochlorothiazide in mice.

There are no adequate and well-controlled studies in pregnant women. VASERETIC® (Enalapril Maleate-Hydrochlorothiazide, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. *Nonteratogenic Effects:* These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: It is not known whether enalapril is secreted in human milk, however, thiazides do appear in human milk. Because of the potential for serious reactions in nursing infants from hydrochlorothiazide, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

VASERETIC has been evaluated for safety in more than 1,500 patients, including over 300 patients treated for one year or more.

In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with enalapril or hydrochlorothiazide.

The most frequent clinical adverse experiences in controlled trials were: dizziness (8.6%), headache (5.5%), fatigue (3.9%), and cough (3.5%). Generally, adverse experiences were mild and transient in nature.

Adverse experiences occurring in greater than 2% of patients treated with VASERETIC in controlled clinical trials are shown below:

	Percent of Patients in Controlled Studies	
	VASERETIC (n = 1,580) Incidence (discontinuation)	Placebo (n = 230) Incidence
Dizziness	8.6(0.7)	4.3
Headache	5.5(0.4)	9.1
Fatigue	3.9(0.8)	2.6
Cough	3.5(0.4)	0.9
Muscle Cramps	2.7(0.2)	0.9
Nausea	2.5(0.4)	1.7
Asthenia	2.4(0.3)	0.9
Orthostatic Effects	2.3(<0.1)	0.0
Impotence	2.2(0.5)	0.5
Diarrhea	2.1(<0.1)	1.7

Clinical adverse experiences occurring in 0.5% to 2.0% of patients in controlled trials included: *Cardiovascular:* Syncope, orthostatic hypotension, palpitations, chest pain, tachycardia. *Nervous System:* Insomnia, nervousness, paresthesia, somnolence, vertigo. *Gastrointestinal System:* Abdominal pain, vomiting, dyspepsia, constipation, flatulence, dry mouth. *Other:* Dyspnea, gout, back pain, arthralgia, hyperhidrosis, pruritus, decreased libido, rash, tinnitus, urinary tract infection. *Angioedema:* Angioedema has been reported in patients receiving VASERETIC (0.6%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy instituted immediately (see WARNINGS). *Hypotension:* In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9%), orthostatic hypotension (1.5%), other orthostatic effects (2.3%). In addition, syncope occurred in 1.3% of patients (see WARNINGS).

Clinical Laboratory Test Findings: *Serum Electrolytes:* See PRECAUTIONS. *Creatinine, Blood Urea Nitrogen:* In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6% of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis (see PRECAUTIONS). *Serum Uric Acid, Glucose, Magnesium, and Calcium:* See PRECAUTIONS. *Hemoglobin and Hematocrit:* Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g % and 1.0 vol %, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. *Other (Causal Relationship Unknown):* Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below: *Enalapril Maleate*—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials, adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Renal:* Renal dysfunction, renal failure, oliguria; *Hematologic:* Rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported in which a causal relationship to enalapril cannot be excluded. *Hydrochlorothiazide—Body as a Whole:* Weakness; *Digestive:* Anorexia, gastric irritation, cramping, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis; *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia; *Musculoskeletal:* Muscle spasm; *Nervous System/Psychiatric:* Restlessness; *Special Senses:* Transient blurred vision, xanthopsia; *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions.

HOW SUPPLIED

No. 3418—Tablets VASERETIC 10-25, are red, squared capsule-shaped, compressed tablets, coded MSD 720 on one side and VASERETIC on the other. Each tablet contains 10 mg enalapril maleate and 25 mg hydrochlorothiazide. They are supplied as follows:

NDC 0006-0720-68 bottles of 100 (with desiccant).

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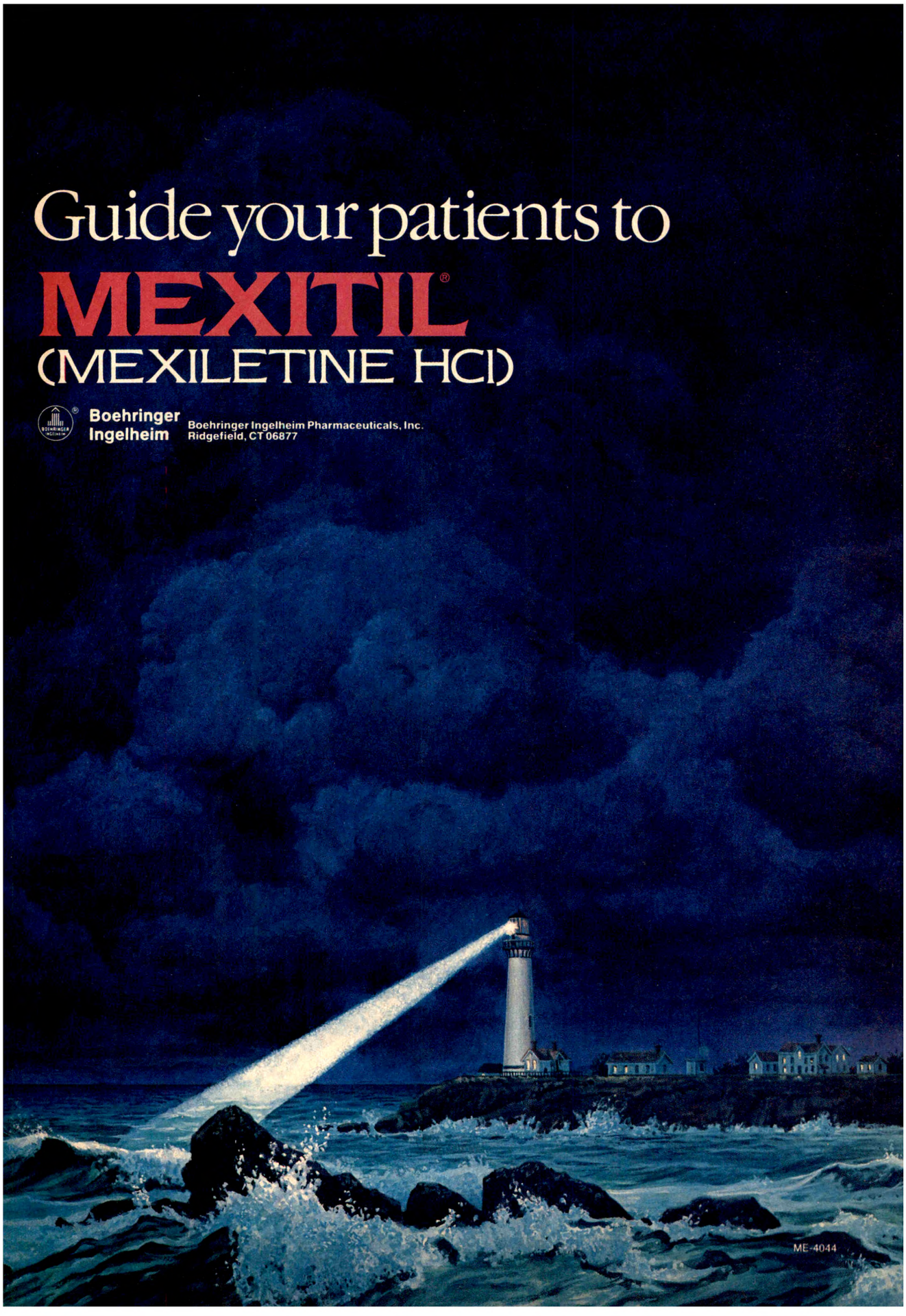

Left Ventricular Dysfunction After Prolonged Strenuous Exercise in Healthy Subjects

DOUGLAS R. SEALS, PhD, MARC A. ROGERS, PhD, JAMES M. HAGBERG, PhD, CHIKASHI YAMAMOTO, MS, PHILIP E. CRYER, MD, and ALI A. EHSANI, MD

To determine whether depressed left ventricular (LV) contractile function can occur after prolonged and strenuous exercise, 12 healthy men, 26 ± 1 years old (mean ± standard error of the mean) were studied. The subjects exercised on a treadmill at 69 ± 1% of maximal O_2 uptake until exhaustion (170 ± 10 minutes). Hemodynamic variables were measured before and 10 minutes aftere exhausting exercise. Baseline systolic blood pressure decreased from 124 ± 2 to 113 ± 3 mm Hg ($p < 0.001$) after exhausting exercise. LV end-diastolic diameter, measured by echocardiography, decreased from 51 ± 1.0 to 47 ± 1.0 mm ($p < 0.005$) but LV end-systolic diameter did not change (34 ± 1.0 vs 34 ± 1.0 mm). Both LV fractional shortening and the mean velocity of circumferential fiber shortening decreased (33 ± 1 vs 28 ± 1%; $p < 0.01$ and 1.09 ± 0.4 vs 0.97 ± 0.05 circ/s; $p < 0.025$) despite a lower end-systolic wall stress (σ_{es} = 88 ± 4 vs 82 ± 5, × 10^3 dynes/cm^2; $p < 0.05$) after prolonged exhausting exercise. A repeat bout of exercise of the same intensity but brief in duration (10 minutes) resulted in increases in LV fractional shortening ($p < 0.001$) and mean velocity of circumferential fiber shortening ($p < 0.001$), and a decrease in LV end-diastolic diameter (50 ± 1.0 to 48 ± 1.0 mm; $p < 0.05$) at heart rates comparable to those attained after prolonged exhausting exercise. The results suggest that prolonged strenuous exercise may result in impaired LV function in healthy young subjects.

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Controversy exists regarding whether strenuous exercise can cause left ventricular (LV) dysfunction in healthy subjects. Earlier studies suggested that impaired LV function might account for the decrease in blood pressure and stroke volume, and inappropriate tachycardia induced by exhausting exercise.[1,2] However, these changes were subsequently attributed to the compensatory thermoregulatory mechanisms that result in a lower effective blood volume which, in turn, can decrease venous return and stroke volume.[3] Some experimental studies also failed to show any evidence for impairment of LV contractile function.[4] On the other hand, there have been reports of depressed LV function after exhausting exercise in rats[5] and a recent study suggested that impaired LV function may occur in well-trained athletes after an ultramarathon (100 km) race.[6] Thus, it is still unclear whether or not strenuous exercise can cause impairment of LV performance. Accordingly, this study examines whether LV dysfunction can occur after prolonged exhausting exercise in young healthy subjects and characterizes the metabolic and hormonal changes concurrent with alterations in LV function.

From the Section of Applied Physiology, Cardiovascular and Metabolism Divisions, Department of Medicine, and the Irene Walter Johnson Institute of Rehabilitation, Washington University School of Medicine, St. Louis, Missouri. This study was supported in part by grant GCRC-RR00036 from the National Institutes of Health, Bethesda, Maryland. Dr. Seals was a postdoctoral Research Trainee supported by Institutional National Service Award AG-00078; Dr. Rogers was a postdoctoral Research Trainee supported by Institutional National Research Service Award HL07456. Manuscript received August 3, 1987; revised manuscript received November 30, 1987, and accepted December 4.

Dr. Seals's current address: Department of Exercise and Sport Sciences, McKale Center, University of Arizona, Tucson, Arizona.

Address for reprints: Ali A. Ehsani, MD, Department of Medicine, Washington University School of Medicine, 4566 Scott Avenue, St. Louis, Missouri 63110.

Methods

Subjects: Twelve male subjects 26 ± 1 years old (mean ± standard error of the mean) volunteered for

the study. They were asymptomatic, had no history of cardiopulmonary disease and their cardiac examination, including 12-lead electrocardiogram and echocardiogram, was normal. None was performing regular endurance exercise. All gave a written informed consent and the study was approved by the Human Studies Committee of the Washington University School of Medicine.

Measurement of maximal O_2 uptake ($\dot{V}O_2$max): A graded treadmill running protocol was used to determine $\dot{V}O_2$max as described by Costill and Fox.[7] $\dot{V}O_2$max was defined as the attainment of a plateau of O_2 uptake with increasing work rates (levelling-off criterion). $\dot{V}O_2$ was measured using an open-circuit gas collection system with a Daniel's breathing valve and neoprene meteorologic balloons. Gas samples were analyzed for O_2 and CO_2 with a Perkin-Elmer MGA-1100 mass spectrometer and the volume of the expired air was measured with a Tissot spirometer as described previously.[8]

Prolonged exercise to exhaustion: The subjects were tested in the morning, 2.5 to 3 hours after a breakfast containing approximately 500 Kcal. A catheter was placed in an antecubital vein and, after 15 minutes of rest, blood was drawn for determination of free fatty acids, catecholamines, lactate and glucose concentrations. Subsequently, an M-mode echocardiogram with simultaneous recording of carotid pulse tracing and measurement of blood pressure using the cuff method was obtained. The subjects walked for 20 minutes on a treadmill at a speed of 3.75 mph and with the grade set to elicit 70% of their $\dot{V}O_2$max. The exercise intensity was then reduced to a speed of 2 mph and 0% grade for 2 minutes. The exercise intensity was then raised to the previous level (70% of $\dot{V}O_2$max) for 18 minutes followed by a 2-minute exercise of reduced intensity. This sequence was repeated for as long as possible. When the subjects were no longer capable of maintaining the initial work rate of 70% of $\dot{V}O_2$max, the exercise intensity was reduced in 0.25 mph and 1% grade decrements and they were asked to continue exercising for at least 10 minutes at each reduced work rate. The onset of fatigue was defined as the time at which the work rate had to be reduced below the initial work rate by 10% of $\dot{V}O_2$max. At that time the exercise was terminated because of exhaustion and the elapsed time was taken as the subjects' endurance time. All subjects were then assisted from the treadmill and placed in a supine position.

The subjects were given water to drink ad libitum throughout the exhausting exercise. $\dot{V}O_2$, heart rate and blood pressure were measured during the last 2 minutes of each 18-minute bout of high intensity exercise. $\dot{V}O_2$ was measured to adjust the work rate to maintain the desired intensity. A repeat echocardiogram and blood samples were obtained 10 minutes after completion of the exhausting exercise.

Brief exercise: Eleven of the 12 subjects returned several weeks later for a repeat treadmill test (the remaining subject was unavailable). The exercise duration was 10 minutes at the same intensity used during the prolonged exercise, that is, 70% of $\dot{V}O_2$max. Blood samples were obtained and echocardiograms recorded before and approximately 5 minutes after the completion of the 10-minute exercise bout. The reason we waited 5 minutes to obtain echocardiograms and plasma samples was that heart rates at that time were comparable to those attained 10 minutes after prolonged exhausting exercise. The brief exercise was performed to determine whether exercise of the same intensity but brief in duration can produce similar hemodynamic and metabolic responses compared with the prolonged exhausting exercise. No complications occurred during or after the 2 bouts of exercise.

Echocardiogram: M-mode echocardiogram and carotid pulse tracings were obtained with a Smith Klein echocardiograph interfaced with a Cambridge strip-chart recorder using the standard approach described previously.[9] The standard landmarks were used for measurements of LV end-diastolic diameter, end-systolic diameter, posterior wall thickness and ejection time (carotid pulse tracing).[9] The same body position and the intercostal space were used for each subject in the 2 trials.

The following parameters were used to examine LV systolic function: (1) end-systolic stress-length relation; (2) LV fractional shortening and (3) mean velocity of circumferential fiber shortening as previously described.[9] Because LV fractional shortening and mean velocity of circumferential fiber shortening are affected by cardiac loading conditions,[10,11] the changes in these variables were examined as a function of estimated end-systolic wall stress. An inverse linear relationship between end-systolic wall stress (σ_{es}) and mean velocity of circumferential fiber shortening has been reported[11] and is considered to be a sensitive index of inotropic state.[11] The meridional end-systolic wall stress was estimated using the following equation: $\sigma = PR/[2h(1 + h/2R)]$, where σ = wall stress; P = systolic blood pressure in grams; h = end-systolic posterior wall thickness; R = LV end-systolic diameter/2.

Assay procedures: One ml of blood was deproteinized in chilled 10% perchloric acid and the neutralized supernatant was assayed for lactate.[12] Plasma glucose was measured using the glucose oxidase method.[13] Three ml of blood was drawn for assay of plasma free fatty acid concentration using the colorimetric method.[14] Four ml of blood was placed in chilled tubes containing 4.5 mg of reduced glutathione, 0.1 ml pargyline and 50 U sodium heparin; the plasma was separated by centrifugation at 4°C and used for determination of norepinephrine and epinephrine by the single-isotope derivative technique.[15] Lactate and glucose concentrations were measured only after the 2.8-hour exercise bout.

Statistics: Student *t* tests for paired observation were used to compare the rest with postexercise data for each exercise protocol. Data are mean ± standard error of the mean.

Results

The subjects' maximal O_2 uptake averaged 3.76 ± 0.12 liter/min (50.1 ± 1 ml/kg/min). $\dot{V}O_2$ during the prolonged strenuous exercise averaged 2.57 ± 0.10 li-

ters/min, which was equivalent to 69 ± 1% $\dot{V}O_2$max. The duration of exercise was 170 ± 10 minutes.

Heart rate and systolic blood pressure: Heart rate during maximal treadmill exercise was 201 ± 3 beats/min. The peak heart rates attained during the prolonged exhausting exercise and the 10-minute exercise were 175 ± 3 and 155 ± 4 beats/min, respectively. Heart rates at rest before the 2 modes of exercise were similar (59 ± 3 and 59 ± 4 beats/min, respectively). The heart rate recorded 10 minutes after the 2.8-hour exhausting exercise was 89 ± 4 beats/min ($p < 0.001$, postexercise vs baseline heart rate). The heart rate 5 minutes after the brief exercise bout was 85 ± 4 beats/min ($p < 0.001$, postexercise vs baseline heart rate). Systolic blood pressure decreased from 124 ± 2 to 113 ± 3 mm Hg ($p < 0.0001$), 10 minutes after the 2.8-hour exercise. In contrast, systolic blood pressure increased from 124 ± 2 to 145 ± 4 mm Hg ($p < 0.001$) after the brief exercise bout.

Changes in left ventricular function and size: Baseline LV fractional shortening was 33 ± 1 and 34 ± 1% before the 2 bouts of exercise. LV fractional shortening was significantly reduced to 28 ± 1% ($p < 0.01$), 10 minutes after exhausting exercise. In contrast, at heart rates comparable to those attained after prolonged exercise, the LV fractional shortening increased to 41 ± 2% ($p < 0.001$) after the brief exercise. Baseline values for mean velocity of circumferential fiber shortening obtained several weeks apart were identical (Figure 1A). It decreased ($p < 0.025$) after the 2.8-hour exhausting exercise but increased ($p < 0.001$) after the brief exercise at comparable heart rates. The decline in LV systolic function following the 2.8-hour exhausting exercise occurred despite a lower average end-systolic wall stress compared with baseline values. The increase in LV systolic function after the short-term exercise was evident even though the average LV end-systolic wall stress was unchanged (Figure 1A). The end-systolic stress-length relation was shifted downward, with a significantly lower end-systolic wall stress and no change in LV end-systolic diameter after exhausting exercise (Figure 2A). In contrast, 10 minutes of exercise at the same intensity shifted this relation to the left with a significantly smaller LV end-systolic diameter (Figure 2A).

Baseline values for LV end-diastolic diameter before the 2 bouts of exercise were 51 ± 1.0 and 50 ± 1.0 mm measured several weeks apart. Ten minutes after the long exhausting exercise, LV end-diastolic diameter decreased to 47 ± 1.0 mm ($p < 0.005$, Figure 1B). Brief exercise resulted in a comparable decrease in this variable, to 48 ± 1.0 mm ($p < 0.05$, Figure 1B) at similar heart rates. LV end-systolic diameter did not change after the 2.8-hour exhausting exercise but decreased significantly after brief exercise (Figure 2). The baseline values for average end-systolic wall stress were similar. However, end-systolic wall stress decreased slightly ($p < 0.05$) after the exhausting exercise but did not change after the 10-minute exercise at comparable heart rate (Figures 1 and 2).

Hormonal and metabolic changes: The increase in plasma norepinephrine concentrations was greater after prolonged exhausting exercise when compared with those following the brief exercise (Table I). There was almost a 4-fold increase from the resting level ($p < 0.01$) in plasma epinephrine concentration after exhausting exercise, compared with only a modest (1.5-fold) increase after the brief exercise ($p < 0.001$).

There was a modest and physiologically insignificant rise in plasma free fatty acids after the brief exercise but a 5-fold increase ($p < 0.001$) after the prolonged exhausting exercise (Table I). Venous plasma lactate was 1.62 ± 0.06 mM after the prolonged exhausting exercise. Plasma glucose concentrations decreased slightly but significantly following the 2.8-hour exer-

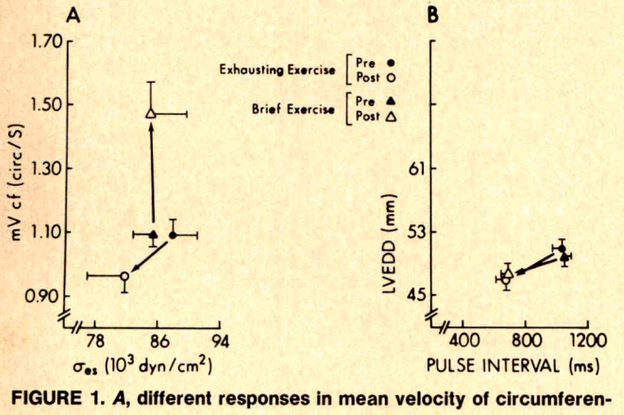

FIGURE 1. *A*, different responses in mean velocity of circumferential fiber shortening (mVcf) after prolonged exhausting and brief exercise at comparable heart rates. Despite a lower end-systolic wall stress, mVcf decreased after strenuous exercise to exhaustion (consistent with depressed contractile state). In contrast, the contractile state was enhanced after brief exercise of the same intensity (relative to $\dot{V}O_2$max), characterized by a large increase in mVcf at comparable levels of wall stress. *B*, at comparable heart rates (pulse interval), the changes in left ventricular end-diastolic dimension (LVEDD) were similar between the 2 bouts of exercise.

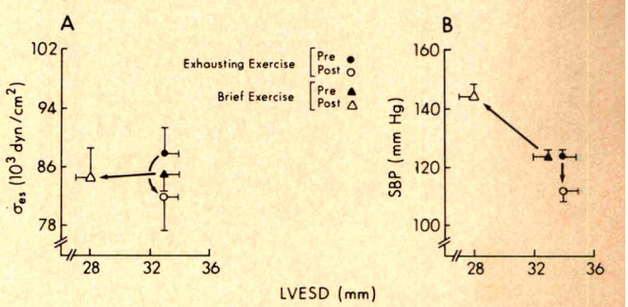

FIGURE 2. *A*, relation between left ventricular end-systolic diameter (LVESD) and end-systolic wall stress (σ_{es}). Prolonged strenuous exercise to exhaustion resulted in a decrease in LVESD with no change in σ_{es}, suggestive of depressed contractile state. Brief exercise of the same relative intensity increased σ_{es} with no change in LVESD, compatible with enhancement of inotropic state. *B*, systolic blood pressure (SBP) decreased following exhausting exercise with no change in LVESD. In contrast, SBP increased ($p < 0.01$) and LVESD decreased ($p < 0.01$) after the brief bout of exercise.

TABLE I Metabolic and Hormonal Changes in Plasma

	Prolonged Exhausting Exercise		Brief Exercise	
	Before	After	Before	After
Norepinephrine (pg/ml)	462 ± 75	726 ± 110 *	202 ± 71	369 ± 99*
Epinephrine (pg/ml)	61 ± 14	233 ± 32*	45 ± 9	65 ± 14*
Free fatty acids (mM)	0.467 ± 0.03	2.449 ± 0.08†	0.420 ± 0.03	0.558 ± 0.04*

* $p < 0.01$ (before versus after); † $p < 0.001$ (before versus after).

cise (83 ± 4 vs 71 ± 2 mM; $p < 0.05$). The hematocrit was virtually identical before and after the exhausting exercise (47.6 ± 0.1 vs 47.6 ± 0.1).

Discussion

The results show that prolonged strenuous exercise leading to exhaustion results in LV dysfunction among healthy young untrained subjects. Ejection phase indexes of contractility are sensitive both to changes in contractility and cardiac loading conditions. Therefore, the lower LV fractional shortening and mean velocity of circumferential fiber shortening observed after prolonged exhausting exercise may result from reduced preload or increased afterload, or both.[10] A decrease in left ventricular end-diastolic diameter in our subjects, therefore, could have accounted for the lower ejection phase indexes of LV function after exhausting exercise. However, the mean velocity of circumferential fiber shortening declined despite a lower end-systolic wall stress reflecting a depressed inotropic state.[11] The changes in end-systolic stress-length relation (lower end-systolic wall stress and no change in end-systolic diameter) were consistent with a decline in LV function.[10,11] Furthermore, the 10-minute bout of exercise that resulted in a comparable decrease in left ventricular end-diastolic diameter caused a marked increase in the ejection phase indexes at heart rates similar to those attained after exhausting exercise. Therefore, our findings are compatible with the interpretation of depressed inotropic state following prolonged exhausting exercise.

The limitations of the M-mode echocardiogram are well recognized. The changes in the LV fractional shortening may not necessarily be representative of global LV function. However, because the subjects were free of cardiac disease and had no chamber enlargement or altered geometry, these limitations should not pose a major problem in the interpretation of our results. The values for end-systolic wall stress should be considered only as estimates because of those known limitations, including the use of peak systolic instead of end-systolic blood pressure. The reproducibility of echocardiographic measurements has been reported previously.[9]

There are several conflicting reports concerning the development of LV dysfunction following strenuous exercise. Sugimoto et al[4] were not able to show depression of LV function. However, Maher et al[5] reported an abnormal force-velocity relation in exhausted rat heart. McKechnie et al[16] reported pulmonary edema in 2 long-distance runners after they participated in an ultramarathon race (100 km). The LV function and coronary angiogram results were normal in both runners. Niemela et al[6] recently found reversible abnormal left ventricular function in competitive runners after an ultramarathon race. The mechanisms underlying left ventricular dysfunction after prolonged exhausting exercise are not clear. Because large concentrations of free fatty acids can cause depression of the inotropic state,[17] impairment of LV function may have resulted, in part, from elevated free fatty acids following prolonged strenuous exercise. The decline in plasma glucose level was too small to account for LV dysfunction. Furthermore, the preferred substrates for oxidative metabolism of the heart are fatty acids.[18] Although plasma norepinephrine concentrations may not necessarily reflect those in the myocardium, impairment of LV function occurred despite higher concentrations of plasma norepinephrine after prolonged (compared with brief) exercise, which may reflect altered sensitivity of LV function to catecholamines.

Although the effects of prolonged strenuous exercise in patients with underlying cardiac disease have not been evaluated, it is possible that exhausting exercise lasting several hours may pose serious potential risks to patients with coronary artery disease. Therefore, engagement in prolonged strenuous exercise without supervision is not advisable in the high-risk population.

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The 24-Hour Heart Rate Behavior in Long-Term Survivors of Cardiac Transplantation

DIMITRIOS ALEXOPOULOS, MD, SALIM YUSUF, MD, DPhil, JIM A. JOHNSTON, BSc, JULIAN BOSTOCK, BSc, PETER SLEIGHT, MD, and MAGDI H. YACOUB, MD

A detailed computerized analysis of heart rate (HR) behavior during ambulatory monitoring was performed in 19 long-term survivors of cardiac transplantation (12 orthotopic, 7 heterotopic) and in 10 normal volunteers. Compared with normal hearts, the transplanted denervated and the recipient innervated hearts in the heterotopic group showed higher average HRs over the whole 24 hours, the waking and sleeping periods. The rates of the denervated and the recipient hearts did not differ significantly. The maximal HR was similar in all 3 groups, but the minimal HR was lower in the normal hearts than in denervated and recipient hearts. The 24-hour RR interval variability was greatly reduced in the denervated hearts (60 ± 22 ms) compared with the recipient (89 ± 26 ms) and normal (151 ± 38 ms) hearts. During arousal from sleep, the magnitude, time and rate of the HR change were significantly reduced in the denervated hearts compared with the innervated hearts and in the recipient compared with the normal hearts. These findings demonstrate that denervated hearts can show significant variations in HR during the 24-hour period, but to a lesser extent than normal hearts. The widest deviation from normal occurs during sleep, when the denervated heart shows minimal slowing probably due to lack of parasympathetic innervation. In heterotopic transplant recipients, the patients' own HR responses also are significantly blunted.

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Although a transplanted heart originates from a young person with a healthy heart, it differs from the normal heart in being anatomically and functionally denervated.[1–3] The response of the denervated heart to dynamic and static exercise has been described previously.[4,5] The 24-hour variations in the heart rate (HR) of the transplanted human heart and its changes during usual daily activities have not been adequately studied. The present study defines the variation in HR over 24 hours after orthotopic and heterotopic cardiac transplantation and compares it with the recipient's own heart—in the case of the heterotopic transplantation—and with normal healthy volunteers.

Methods

Study population: Nineteen transplant recipients who survived >6 months were studied. Twelve men (mean age 45 ± 9 years) had orthotopic cardiac transplantation 20 ± 10 months earlier and 7 patients (6 men, 1 woman, mean age 39 ± 8 years) had heterotopic cardiac transplantation 11 ± 3 months earlier, with the donor heart inserted in parallel to the recipient's heart. Surgical techniques were described elsewhere.[6,7] Most patients were receiving a mixture of azathioprine, cyclosporine, prednisolone, aspirin, dipyridamole and diuretic. All patients were asymptomatic and performed their usual physical activities. Signs of mild rejection were present in the most recent cardiac biopsy in only 2 of the patients whereas the remaining patients had no evidence of rejection. Ten normal volunteers, 5 men and 5 women (mean age 38 ± 10 years), served as a control group. All were asymptomatic with normal physical examination and resting electrocardiogram.

Electrocardiogram recordings: Twenty-four-hour Holter monitoring was performed using a 2-channel recorder (Oxford Medilog II or MR14). The leads (modified V_1 and V_4) were recorded. In heterotopic transplants a modified V_{4R} lead was used, instead of V_1, to allow the optimal separation of QRS between donor and recipient hearts. The patients were provided with a diary to record all their symptoms and activities, and were not restricted in any way.

Heart rate analysis: Dual channel analysis was performed using a computerized, nontriggered, tem-

From John Radcliffe Hospital, Oxford, and Harefield Hospital, Harefield, Middlesex, England. Manuscript received September 8, 1987; revised manuscript received and accepted November 24, 1987.

Dr. Alexopoulos's present address: Mount Sinai Medical Center, 1 Gustave L. Levy Place, New York, New York 10029. Dr. Yusuf's present address: 604 Federal Building, National Heart, Lung, and Blood Institute, Bethesda, Maryland 20205.

Address for reprints: M.H. Yacoub, MD, Harefield Hospital, Harefield, Middlesex, England UB9 6JH.

plate system able to classify the beats into many families. The system consisted of a Z80A preprocessor and a DEC LSI-11 master. The tapes from patients with heterotopic transplantation were analyzed twice in order to quantify separately the variations in HR in the donor and the recipient hearts. An example of a recorded electrocardiogram is presented in Figure 1.

The data were analyzed to obtain: (1) the 24-hour HR trend, with each point representing the mean HR over 1 minute. Maximal and minimal HR (minute averages) were measured; (2) a histogram (with mean value and standard deviation) of all the RR intervals observed over 24 hours; (3) the mean HR every hour; (4) the RR intervals—printed on a Medelec fiberoptic recorder (FOR-4.2) for 20 minutes before and after the time of waking. The HR change was measured using the RR change from the onset of arousal to the persistently lowest RR in the next 5 minutes. The change in HR over time was expressed as the rate of HR change.

All values are expressed as mean ± 1 standard deviation. Statistical analysis was performed using Student *t* test (paired or unpaired, as needed).

Results

The interval between operation and study was longer in the orthotopic than the heterotopic transplantation group ($p < 0.025$). Sleeping and waking times were similar in the 3 groups. Because a comparison of all studied parameters between the donor hearts in the 2 groups of orthotopic and heterotopic transplantation revealed no differences, they were analyzed as a single group.

Twenty-four-hour heart rate changes: The overall HR variation is shown in Figure 2. The mean HR for corresponding hours was higher in donor and in recipient hearts than in normal hearts, but not significantly different between donor and recipient hearts. When the 24 hours were considered as a whole, a higher HR was found in donor compared with recipient hearts ($p < 0.001$). The mean 24-hour, daytime and sleep HRs were higher in donor and recipient hearts compared with normal ones (Table I). The differences between donor and recipient hearts were not significant. There was a significantly wider separation between donor versus normal and recipient heart rates during sleep compared with daytime ($p < 0.001$ for both, Figure 2).

Maximal and minimal heart rate: The maximal HR was similar in the 3 groups (Table I). The minimal HR was higher in donor and in recipient compared with normal hearts. The difference between donor and recipient hearts was not significant.

Heart rate variability: The HR variability, as indicated by the standard deviation of the 24-hour mean RR interval, was reduced in donor hearts (60 ± 22 ms) compared with both recipient (89 ± 26) and normal (151 ± 38) hearts ($p < 0.02$ and $p < 0.001$). In recipient hearts, the HR variability was less than normal ($p < 0.005$). Examples of the RR interval histograms are presented in Figure 3.

Heart rate changes during waking: The HR increases in donor and in recipient were lower than normal during this period (Table II). Although donor hearts showed less change when compared with recipient hearts, there was no statistically significant difference. However, within the heterotopic transplantation group alone, HR changes were lower in the donor than the recipient heart (12 ± 4 vs 20 ± 6 beats/min, $p < 0.05$). These HR changes took longer to complete in

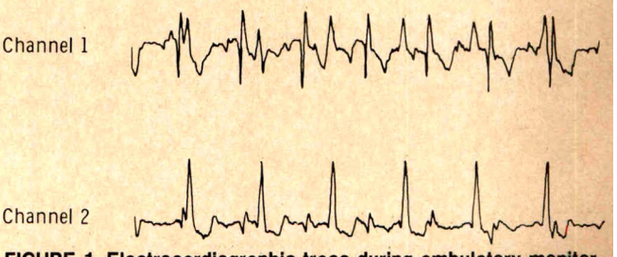

FIGURE 1. Electrocardiographic trace during ambulatory monitoring after heterotopic transplantation. Channel 1: Donor QRS complex dominant. Channel 2: Recipient QRS dominant. Although the difference in QRS amplitude in Channel 1 was not great, clear separation was achieved by pattern recognition.

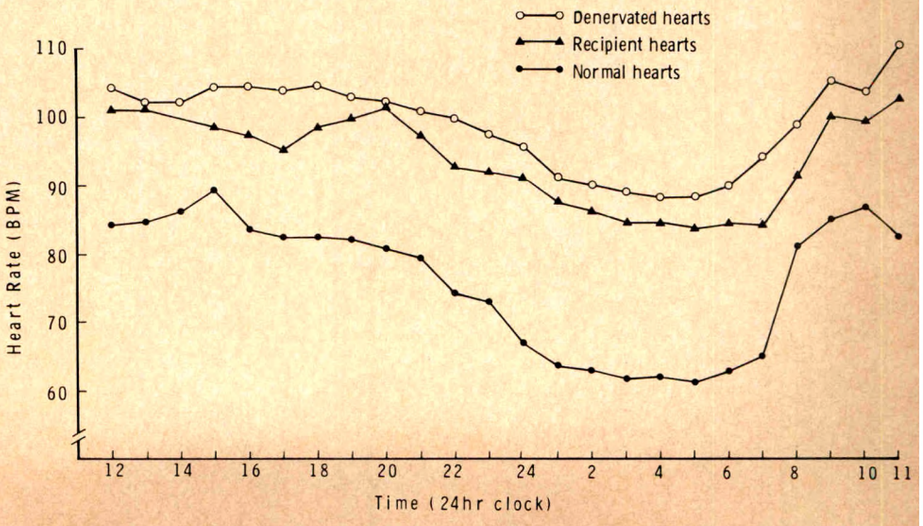

FIGURE 2. Overall pattern of 24-hour heart rates for each group.

TABLE I Mean 24-Hour, Daytime and Sleep Heart Rates, and Maximal and Minimal Heart Rates in Donor, Recipient and Normal Hearts

Heart	24-Hour HR	Daytime HR	Sleep HR	Max HR	Min HR
D	99 ± 11*	104 ± 11*	90 ± 12*	123 ± 14	82 ± 12*
R	96 ± 13†	100 ± 14‡	86 ± 11*	122 ± 13	74 ± 11§
N	77 ± 10	83 ± 12	63 ± 7	127 ± 13	58 ± 9

* $p < 0.001$; † $p < 0.01$; ‡ $p < 0.025$; § $p < 0.005$. All p values refer to comparison versus N.
D = donor; HR = heart rate; Max = maximal; Min = minimal; N = normal; R = recipient.

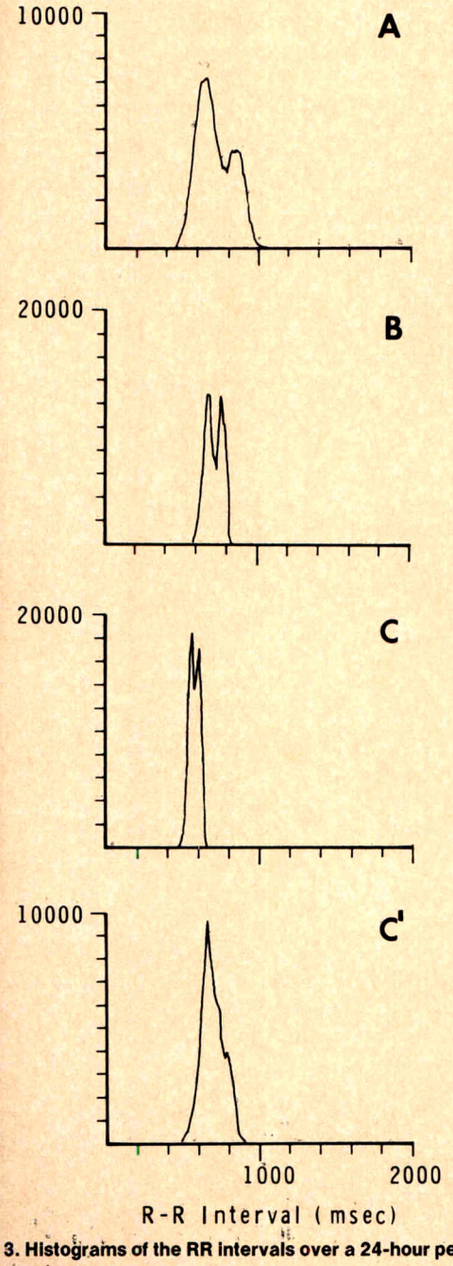

FIGURE 3. Histograms of the RR intervals over a 24-hour period in a normal volunteer (*A*), an orthotopic transplantation patient (*B*) and an heterotopic transplantation patient (*C*), donor heart and (*C'*) recipient heart. Note the narrower base of the denervated hearts' histograms (*B* and *C*).

TABLE II Heart Rate Changes During Waking in Donor, Recipient and Normal Hearts

	HR Increase (beats/min)	Time of HR Change (s)	Rate of Change (beats/min/min)
D	16 ± 9	219 ± 201	7 ± 5
R	20 ± 7	75 ± 30	20 ± 13
N	35 ± 9	33 ± 25	82 ± 38
p Values			
D vs N	0.001	0.001	0.001
R vs N	0.01	0.01	0.001
D vs R	NS	0.01	0.02

NS = not significant. Other abbreviations as in Table I.

donor than in recipient and normal hearts, and in recipient compared with normal hearts (Table II). Examples of these changes are given in Figures 4 and 5. All the studied parameters were independent of the age of the donor and recipient heart or the interval between the operation and the study.

Discussion

The transplanted heart offers a unique model for studying the hormonal and intrinsic control of the heart.[8] Heterotopic transplantation, with the existence of 2 hearts—denervated and innervated—is ideal for studying the behavior and reactions of the same organ to different stimuli with and without neural control.

Although Holter monitoring has been performed previously after orthotopic cardiac transplantation for detection of arrhythmias,[9,10] there is no previous detailed report concerning the 24-hour HR behavior of the transplanted heart. To our knowledge, continuous HR monitoring has not been described at all in patients following heterotopic heart transplantation. The responses to different stimuli of the remnant atria after orthotopic transplantation have been reported previously,[11,12] but the small amplitude of the recipient atrial P wave does not allow its Holter analysis. With the system we used (based on QRS-pattern recognition), we analyzed separately the ventricular electrical activity of the 2 hearts in the heterotopic transplants even when the 2 QRS complexes were of similar amplitude, which would defeat a QRS-triggered system.

The resting HR of the denervated heart is known to be elevated.[13,14] Our findings of higher mean 24-hour, waking and sleep HRs in the denervated hearts sup-

port this. The innervated recipient's own heart was significantly faster than the normal heart. Part of the increase in HR of the recipient's own heart may be due to elevated circulating catecholamines. Parasympathetic dysfunction[15] of the recipient heart may have also contributed to its higher than normal rate.

The maximal recorded HR during the 24-hour period was similar in the denervated and the innervated hearts and is consistent with previous studies[16] of HR responses of transplanted hearts to dynamic exercise. Following heterotopic transplantation the peak HR achieved during maximal dynamic exercise is almost identical in the donor and the recipient hearts.[7] The minimal HR was higher in the denervated hearts, mainly due to the absence of vagal innervation. The higher minimal HR in the recipient hearts may have been due to parasympathetic dysfunction of the diseased hearts or elevated circulating catecholamines.[17]

The 24-hour variability was reduced in the denervated hearts, largely due to the inability to achieve low HRs. A reduced variation in the resting cycle length of the denervated hearts has been reported previously.[18] By contrast, recipient hearts and normal control hearts demonstrated more HR fluctuation. The gradual changes seen during waking up were similar to the slower increase in HR of the denervated hearts during the early exercise stages.[16] An autonomic dysfunction of the diseased recipient hearts may explain the differences with normal subjects.[19,20] In contrast to our results, Guilleminault et al[21] have reported 7 orthotopic transplants with time courses and magnitudes of HR variation similar to those of normal subjects.

The underlying mechanisms that account for the blunted HR responses of the denervated and, to a lesser extent, the recipient innervated hearts, are certainly quite complex and not fully understood. Supersensitivity of the denervated heart to circulating catecholamines[22] or abnormalities related to damage originated during the donor's death, removal, preservation and implantation procedure, rejection episodes[23] and accelerated atherosclerosis[24] may be involved.

All patients were receiving drugs that might have influenced our results,[25] although the observed differences between the donor and the recipient hearts cannot be explained in this way because the medication was similar in all patients. In the long term, the behavior of the transplanted hearts may change due to adaptation, conditioning and possibly reinnervation.

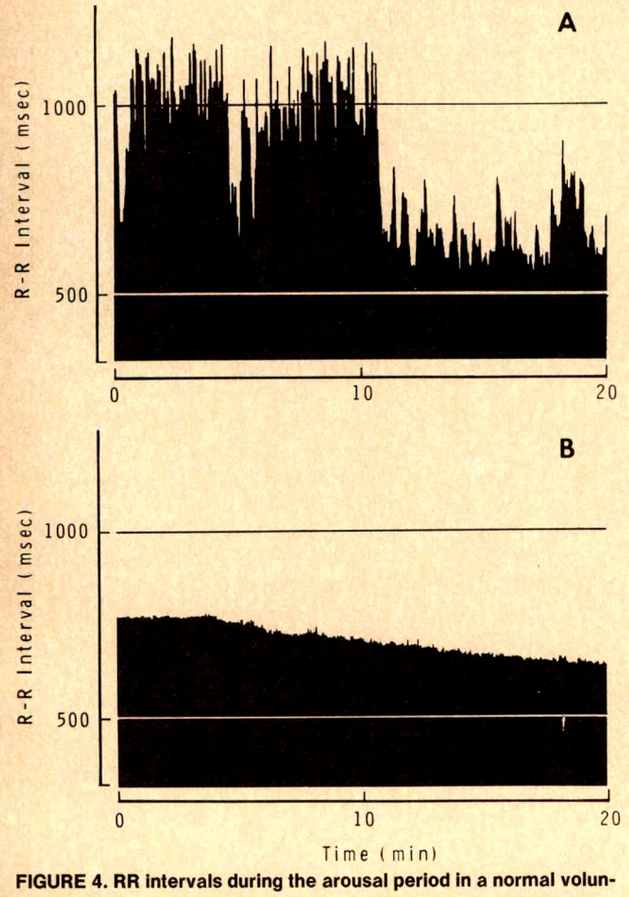

FIGURE 4. RR intervals during the arousal period in a normal volunteer (*A*), and an orthotopic transplantation patient (*B*). Note the smooth appearance in *B*, in contrast to the spiky appearance in *A*, reflecting the lack of beat-by-beat variability in the denervated heart.

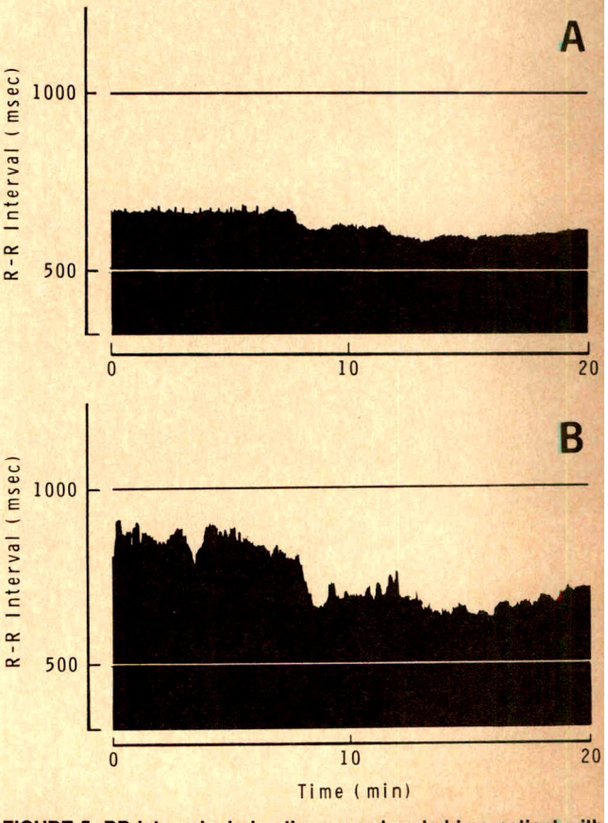

FIGURE 5. RR intervals during the arousal period in a patient with heterotopic transplantation. *A* = donor heart; *B* = recipient heart.

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Optimal Lead Subsets for Reconstruction of QRS and ST-T in 35-Lead Precordial Maps

CHRISTOPHER D. McMANUS, MA, ALAN S. BERSON, PhD, JORGE C. RIOS, MD, EMIGDIO A. LOPEZ, MD, and HUBERT V. PIPBERGER, MD

Precordial maps have been used for some 15 years to estimate the extent of myocardial injury in patients with acute anterior or lateral wall infarction. Estimates have been based on various QRS- and ST-T-derived parameters, including amplitude sum of ST elevations. Application of the electrodes, commonly 35, is cumbersome and time-consuming with the critically ill. A subset of 5 or 7 selected leads can be applied instead, and the remaining leads calculated from that subset with minimal loss of QRS and ST-T information. Maps were recorded from 100 patients within 72 hours of onset of anterior or lateral infarct. Optimal lead subsets for QRS and ST-T feature extraction were found by the sequential selection method of Lux. Subsets numbering between 2 and 15 leads were derived, with their lead-transform coefficients. Measures to estimate goodness of fit for reconstructed leads included correlations, error-to-signal ratios and root-mean-square errors. These measures were calculated separately over the QRS and ST-T complexes. Reconstructions from a 7-lead subset had a mean 0.92 correlation with ST-T in the original leads and root-mean-square error of only 0.04 mV. Sum of ST elevation differed by only 2% between original leads and reconstructions based on 5 or more leads. To confirm repeatability, lead-transform coefficients were also calculated from a training population of 50 patients and applied to the maps of the other 50.

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A new electrocardiographic technique to estimate the size of anterior wall myocardial infarcts was introduced in 1971 by Maroko,[1] Reid[2] and their co-workers. Arrays of electrodes are applied to the precordial area. The degree of ST-segment elevation in these leads is interpreted as an indicator for the extent of myocardial injury. In patients with acute myocardial infarction, serial precordial maps have also often been used to estimate increases or decreases of the injured myocardial area.

Problems with the underlying assumptions have been reviewed in detail by Holland and Brooks.[3] Nevertheless, the simplicity of the method and its noninvasive nature have led to its acceptance as a tool to estimate infarct size and to evaluate therapeutic interventions. In recent years, the number of leads was standardized to 35, based on the suggestion of Maroko et al.[4]

Application of large arrays of electrodes over the precordium is cumbersome and time-consuming. Past studies suggest that the information in precordial maps is contained in subsets of many fewer leads, since neighboring leads contain much redundant information. Akiyama et al[5] compared ST findings in precordial maps with those seen in Frank orthogonal 3-lead recordings. A correlation of 0.818 was found between maps and the Frank leads and the latter were considered adequate for ST-segment studies. In dog experiments, Foerster et al[6] found an even higher correlation between ST changes in precordial maps and orthogo-

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Dr. Berson's present address: National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Address for reprints: H.V. Pipberger, MD, Department of Computer Medicine, The George Washington University School of Medicine, 2300 K Street, Northwest, Washington, DC 20037.

nal leads (r = 0.921). These high correlations confirm more basic studies on the "dipolar" behavior of ST and T potentials.[7,8]

In contrast to ST-T complexes, QRS potential distributions have not followed simple dipolar patterns in studies based on total body surface maps. Several precordial mapping studies[9,10] have used QRS-derived parameters to estimate infarct size; thus, any study on lead reduction must also consider the QRS complex.

We obtained complete precordial maps from patients with acute anterior and lateral infarcts, and applied data reduction techniques in order to identify a small subset of leads that would allow reconstruction of the QRS and ST-T complexes of the original 35 leads. Once such a subset has been identified from a sufficiently large base, only a small number of electrodes need to be applied to future patients with acute infarcts to derive full precordial maps.

Methods

Patients with acute anterior or anterolateral infarcts were selected by staff physicians in the coronary care units of George Washington University Hospital, Washington, DC, and Brigham and Women's Hospital, Boston, Massachusetts. Patients in this study from the latter hospital were selected from subjects in the Multicenter Investigation of the Limitation of Infarct Size study.[11] Only patients with anterior or anterolateral infarcts were included because precordial mapping is thought to provide a measure of myocardial ischemia and injury of the myocardium underlying the anterior and lateral chest wall. Diagnosis was based on clinical history, enzyme elevations and acute ST elevations in anterior and lateral precordial leads of the standard 12-lead electrocardiogram. Informed consent was obtained from patients and their attending physicians. Patients with other conditions that lead to ST elevations were excluded. The first record was taken as soon as possible after admission to the coronary care units, because ST abnormalities subside in some patients relatively soon after the acute event. Patients who did not exhibit ST abnormalities on admission were excluded from further study.

The recording procedure was reduced to less than 15 minutes by use of a flexible plastic sheet with 35 holes set in 5 rows for the electrodes. Distances between electrodes were set to the specifications of Maroko et al.[4] The area covered by the precordial map extends from the left midaxillary line to a vertical line to the right of the sternum corresponding to the position of the conventional lead V_1. In some patients the electrodes consisted of small disks of lithium chloride-impregnated balsa wood cemented to the silver/silver-chloride surface of Becton Dickinson-type electrodes. The contact of the balsa wood with the skin eliminates the need for electrode paste, which usually prolongs and complicates the recording procedure.[12]

Maps were recorded using model 2001 mobile carts (Instruments for Cardiac Research). Cart features include: 500 sample/s recording and storage of 12 simultaneous potentials on magnetic tape cassette; input impedance from each patient lead to ground and between any 2 leads >50 megohms; right leg lead used as driven ground; leakage currents <10 μV through use of an isolated battery-powered front end. All other safety and performance characteristics met or exceeded American Heart Association specifications.[13] The 35 electrodes were connected to a switchbox that allowed simultaneous transmission of 12 leads. One standard limb lead (II) was recorded continuously as a time reference. Standard-lead and Frank orthogonal-lead electrocardiograms were also recorded on all patients at the time of their mapping.

Precordial maps were recorded on 124 patients. Data analysis was performed at the Veterans Administration Medical Center in Washington, DC. System noise was first measured on each lead of each map. Mean system noise over all leads was 19 μV. Patients with noise on any lead exceeding 70 μV were excluded. Finally patients whose tracings had no signal ("dropout") in any lead were excluded. There remained 100 tracings for study: 86 from Brigham and Women's Hospital and 14 from George Washington University Hospital.

The maps were reduced to 1 time-aligned heart cycle per patient, using the wave-recognition algorithms of the Pipberger vectorcardiographic analysis program.[14] The algorithms were applied to 3 leads from each lead set, in order to obtain a representative cycle ("best beat") on that lead set. Beats found by this method have been shown to be especially free of respiratory influence and have high reproducibility.[15] QRS onsets in leads of different lead sets were aligned by cross-correlations between the reference lead QRS complexes in successive lead sets.

For selection of reduced lead sets, we used a method developed by Lux et al.[16] Their statistical approach involves no assumptions about the nature of the heart as an electric generator. The method first derives a set of equations for the best coefficients to apply to any chosen lead subset to approximate the potentials of the remaining leads. The surface potentials at each instant are treated as an n-dimensional random vector, P.

The vector P can be reordered and partitioned into an m-dimensional vector P_1 and an (n-m)-dimensional vector P_2. This process also partitions the covariance matrix K associated with P into:

$$K = \begin{bmatrix} K_{11} & K_{21} \\ K_{12} & K_{22} \end{bmatrix}. \quad (1)$$

If T represents the transformation that optimally estimates P_2 from P_1, then the mean-squared error J between the original and estimated lead values is minimized if $T = K'_{12}K_{11}^{-1}$. (2)

The method of Lux secondly develops a recursive algorithm for selecting the m lead locations to derive the remaining leads with least error, for any number m. From equation 2, the mean-squared estimation error J due to the transformation T is:

$$J = \mathrm{tr}(K) - \mathrm{tr}(K_{11}) - \mathrm{tr}(K'_{12}K_{11}^{-1}K_{12})$$
$$= \mathrm{tr}(K) - \mathrm{tr}(K_{11}^{-1}L_{11}), \quad (3)$$

where tr is the matrix trace operator and

$$L_{11} = K_{11}K_{11} + K_{12}K'_{12}. \quad (4)$$

TABLE I Mean Values of Goodness of Fit Measures to Assess Performance of Different Numbers of Optimal Leads for Reconstructing 35-Lead Maps (Optimal Leads Were Selected Separately for QRS and ST-T Complexes)

	Leads								
	2	3	5	7	9	12	15	Frank 3	Standard 12
QRS reconstruction									
Correlation coefficient	0.81	0.89	0.94	0.95	0.96	0.97	0.97	0.80	0.85
Root-mean-square error (mV)	0.23	0.16	0.12	0.10	0.10	0.08	0.08	0.23	0.19
Error-to-signal ratio	0.22	0.11	0.06	0.04	0.03	0.02	0.02	0.37	0.19
ST-T reconstruction									
Correlation coefficient	0.83	0.88	0.90	0.92	0.92	0.94	0.94	0.80	0.82
Root-mean-square error (mV)	0.06	0.05	0.04	0.04	0.03	0.03	0.03	0.07	0.06
Error-to-signal ratio	0.18	0.12	0.07	0.06	0.05	0.03	0.03	0.35	0.20

Since tr(K) cannot be changed, J is minimized when we maximize the "information index" $I = tr(K_{11}^{-1}L_{11})$. If the lead set P_1 is a single site j, then

$$K_{11}^{-1} = 1/s_j^2,\ L_{11} = \Sigma_i s_i^2 s_j^2 r_{ij}^2,$$

$$\text{and } I_j = tr(K_{11}^{-1}L_{11}) = \Sigma_i s_i^2 r_{ij}^2,$$

where s_i and r_{ij} are the standard deviation at site i and the correlation coefficient between sites i and j, respectively.

This single-lead selection method is incorporated into a simple sequential selection algorithm, as follows. Having selected a best lead j, consider the remaining (n-1) lead sites as a vector P, and find the lead k with maximal information index I_k for that vector. Recursively, after each lead selection, consider the remaining leads as a vector P, and find the site l with maximal index I_l for that vector. This procedure provides at each step both a specific lead set and a measure of the information content of the selected leads, so that a limit on acceptable estimation error can be preset and used to terminate the procedure. The algorithm is optimal in the sense that no other set of m leads has smaller error, although the set is not necessarily unique; i.e., other lead sets might have equal error.

The coefficients necessary to estimate or "reconstruct" the remaining leads from a chosen set are simply the entries of the transformation operator T from equation 2. Following Lux, the estimation error was expressed in 3 parameters: mean correlation coefficient, which characterizes similarity in lead patterns but not in amplitudes; ratio of error strength to signal strength, which characterizes both lead configuration and amplitude; and root-mean-square error. Their equations are, respectively:

$$r = X'Y/|X||Y|; \quad (5)$$

$$\text{ratio} = |X - Y|^2 / |X|^2; \quad (6)$$

$$\text{and } E = |X - Y| / n^{1/2}, \quad (7)$$

where X and Y are the original and reconstructed time sequences of a lead site, and n is the sequence length. For each reconstruction, these 3 measures were calculated for each estimated lead, to get the average value of each measure over all estimated leads.

Because QRS has been included in some estimates of infarct size,[9,10] the data reduction project was divided in 2 parts, one for QRS and one for ST-T. As expected, 2 sets of optimal leads resulted from this division of the study, with comparable accuracy from a smaller subset for ST-T studies and a slightly larger one for QRS. For practical reasons, a common set was also determined for both QRS and ST-T.

TABLE II Measures of Agreement Between Sum of R-Wave Amplitude (ΣR) in Original Precordial Maps and Maps Reconstructed from Different Numbers of Optimal Leads

	5-Lead Basis	7-Lead Basis	9-Lead Basis
Mean difference between ΣR of original and reconstructed maps (mV)	−0.15	−0.06	0.17
Difference as percent of original ΣR amplitude	−1%	0%	1%
Correlation coefficient between original and reconstructed ΣR	0.97	0.97	0.98

Mean ΣR in the original maps was 13.54 ± 1.11 mV (standard deviation).

Results

Final study data were lead values from a single, computer-determined QRS-T complex, over 35 leads, for each of 100 acute infarct patients. Lead subsets numbering between 2 and 15 leads were selected for their power in reconstructing the original 35-lead maps. In addition, the standard 12 leads and 3 orthogonal Frank leads were also tested for their power in reconstructing the total map. Using the aforementioned transformation method, the smaller lead sets served as bases for reconstruction of the original QRS and ST-T complexes.

Typical results, separated for QRS and ST-T, are listed in Table I. Reconstructing the QRS complex from only 2 leads resulted in a mean correlation coefficient of 0.81 between the original and reconstructed leads. With an increasing number of leads, this correlation coefficient rose to 0.97 when 12 leads were used for the reconstruction. Mean correlation coefficients for Frank leads were close to those obtained from 2 optimized leads. For the standard 12 leads, correlations were found to be in between 2 and 3 optimized leads. The mean root-mean-square error decreased from 0.23 mV for reconstructions from 2 leads to 0.08 mV for 12 leads. Corresponding mean root-mean-

TABLE III Measures of Agreement Between Sum of ST-T Elevations (ΣST) in Original Precordial Maps and Maps Reconstructed from Different Numbers of Optimal Leads

	3-Lead Basis	5-Lead Basis	7-Lead Basis	9-Lead Basis	12-Lead Basis
Mean difference between ΣST of original and reconstructed maps (mV)	−0.34	−0.07	−0.10	−0.09	−0.06
Difference as percentage of original ΣST amplitude	−6%	−1%	−2%	−1%	−1%
Mean difference between number of leads with ST elevation >0.1 mV (± SD)	−0.6 ±4.4	0.1 ±2.2	−0.3 ±1.7	−0.2 ±1.4	−0.5 ±1.3
Correlation coefficient between original and reconstructed ΣST	0.95	0.97	0.98	0.99	0.99

Mean ΣST in the original map was 5.51 ± 3.77 mV (standard deviation [SD]) at 40 ms after the J point.

TABLE IV Mean Values of Goodness of Fit Measures to Assess Performance of Different Numbers of Optimal Leads for Reconstructing 35-Lead Maps (Optimal Leads Were Selected Separately for QRS and ST-T Reconstruction, Based on a 50-Patient Training Set; Reconstructions from the Optimal Lead Sets Were Then Applied to the other 50 Patients as a Test Set)

	5 Lead		7 Lead		9 Lead	
	Train Set	Test Set	Train Set	Test Set	Train Set	Test Set
QRS reconstruction						
Correlation coefficient			0.95	0.95	0.96	0.96
Root-mean-square error (mV)			0.10	0.11	0.09	0.10
Error-to-signal ratio			0.04	0.04	0.03	0.04
ST-T reconstruction						
Correlation coefficient	0.90	0.90	0.92	0.92	0.92	0.92
Root-mean-square error (mV)	0.04	0.04	0.04	0.04	0.03	0.04
Error-to-signal ratio	0.07	0.08	0.05	0.07	0.04	0.05

TABLE V Mean Values of Goodness of Fit Measures That Assess Performance of Different Lead Subsets for ST-T Reconstruction. Results in Columns Marked a Refer to Lead Bases Chosen from ST-T-Derived Statistics; Results in Columns b Refer to Lead Bases Chosen from QRS-Derived Statistics (Optimal Lead Bases Chosen from Either QRS or ST-T Data Allow Reconstruction of ST-T Features Nearly Equally)

	3 Lead		7 Lead		9 Lead		12 Lead		15 Lead	
ST-T Reconstruction	a	b	a	b	a	b	a	b	a	b
Correlation coefficient	0.88	0.88	0.92	0.90	0.92	0.92	0.94	0.93	0.94	0.93
Root-mean-square error (mV)	0.05	0.05	0.04	0.04	0.03	0.04	0.03	0.03	0.03	0.03
Error-to-signal ratio	0.12	0.12	0.06	0.07	0.05	0.05	0.03	0.04	0.03	0.03

square errors for the Frank and standard 12 leads were 0.23 and 0.19, respectively. Mean error-to-signal ratio was 0.22 for 2 leads and decreased to 0.02 for reconstructions from 12 optimized leads. For the Frank leads and the standard 12 leads, corresponding error-to-signal ratios were 0.37 and 0.19.

Reconstruction of the ST-T complex was slightly more efficient. The mean correlation coefficient increased from 0.83 to 0.94 when the number of leads was increased from 2 to 12. Mean root-mean-square error decreased from 0.06 mV with 2 leads to 0.03 mV when 9 leads were used. Mean error-to-signal ratio decreased from 0.18 for 2 leads to 0.03 with 12 leads. Reconstruction of the ST-T complex from Frank leads or standard 12 leads gave results similar to those found in the QRS complex. Results were even slightly worse than reconstructions based on 2 optimal leads selected from the original 35 lead set.

Comparisons between amplitude sums of original maps and reconstructed maps are listed in Tables II and III. For maps reconstructed from 5 or more optimal leads, the mean differences between R-wave voltage sums in original and reconstructed maps amounted to an insignificant 1% of the original R-wave amplitude sums. Correlation coefficients between original and reconstructed R-wave sums varied from 0.97 to 0.98. The sums of ST amplitudes were compared at 40 ms after the end of QRS. For maps reconstructed from

5 leads or more, the mean differences between sums of ST amplitudes in original and reconstructed maps were only 1 to 2% of the original ST-amplitude sums. Correlation coefficients between original and reconstructed ST-segments sums were high, increasing from 0.95 to 0.99 when the number of leads was increased from 3 to 9.

To test repeatability of results, the original 100 maps were divided into a training set of 50 maps and a test set of 50. Results from the training and test sets are listed for both QRS and ST-T in Table IV. A comparison of training and test sets shows results that are extremely stable with only very small differences.

Optimal lead locations determined for QRS and ST-T reconstruction are clearly not unique. Due to the short distances between electrodes and consequent high degree of redundancy between neighboring electrodes, a shift from 1 location to an adjacent one may lead only to minute changes in reconstruction. This lead redundancy makes practical a common set of reduced leads for both QRS and ST-T reconstruction. To confirm this redundancy, the original optimized lead sets for QRS were replaced by those of ST-T. This was also done in reverse order. Results are listed in Table V. As can be seen, reconstruction of QRS and ST-T complexes results in almost identical records when optimized lead sets for QRS are replaced by optimized sets for ST-T. Only minute differences in the second decimal position could be found. This indicates that optimal lead sets for QRS can be safely replaced by those obtained for ST-T.

Recommended lead locations for reduced lead sets are shown in Figure 1. Locations are valid for both QRS and ST-T reconstruction. Locations are widely spread with a slightly higher concentration of leads close to the sternum and a smaller number over the left precordium. Lead locations of the full precordial map are shown for comparison.

Discussion

The performance of optimal lead sets of various sizes is shown in Table I. As shown, mean correlation coefficients, root-mean-square errors and error-to-signal ratios are all unchanged when the number of electrodes in the optimal lead subset is increased above 12. In fact, improvement is only minimal when the subset is increased above 5 or 7 leads. For practical purposes, these smaller sets appear adequate for reconstructions.

Lux et al[16] used, as error limits for recomputing total body surface maps of 192 leads from a reduced set of 30 leads, an average root-mean-square error of 32 μV, average correlation coefficient of 0.983 and an error-to-signal ratio of 3.5% in the presence of 20 μV-system noise. Our error limits for QRS and ST-T reconstruction (Tables I, IV and V) significantly exceed their limits. Comparisons are misleading, however, because their reconstruction involved total body surface maps while our study is restricted to chest leads, which are nearest the center of cardiac electrical changes. Also, their study measured reconstruction errors over the entire cardiac cycle, while our study measured error only in the QRS and ST-T complexes, where amplitude changes are greatest.

In practical applications, the proper locations for the electrode subset can be easily determined. For the 7-lead optimal subset, for example, the first electrode is placed in the fourth intercostal space, on the right side of the sternum. On the left sternal border, 1 electrode is placed in the third intercostal space and 1 in the sixth. To determine the remaining locations, one must measure the horizontal distance between the left anterior axillary line and a vertical line following the left sternal border. One electrode each is placed at one-fourth of this measured distance, at the horizontal level of the second and of the fourth intercostal spaces. The next electrode is placed at three-fourths of the measured distance in the sixth intercostal space. The last electrode is placed in the left anterior axillary line, in the third intercostal space. When applying only 5 optimal leads, the same locations are used, but the 2 electrodes on the left sternal border are omitted.

The present recording procedure, involving 35 electrode sites, is cumbersome and time-consuming. When interpreted by human observers, repeat variability is large. Our study has shown that QRS-T information in the 35 electrode array can be reconstructed from a smaller set of 5 to 7 leads. Coefficients to transform these lead subsets to signal values in the remain-

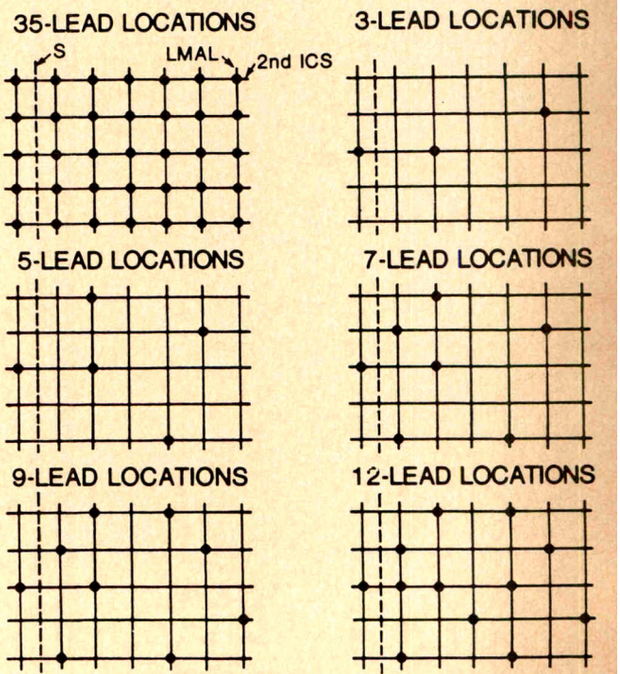

FIGURE 1. Optimal lead locations for reconstruction of the QRS-T component of precordial maps. *Top left*, the original 35 lead locations, with the sternum (S), left mid-axillary line (LMAL) and second intercostal space (2nd ICS) marked. The *bottom row* of this map is the sixth intercostal space. The other 5 figures show the optimal lead locations for reconstructing the precordial map from 3, 5, 7, 9 and 12 leads, respectively. Lead locations were chosen by a sequential algorithm. Thus, larger lead sets include the smaller sets.

ing leads are available by writing the authors. It is hoped that this data reduction will result in a more practical clinical method for studies of myocardial infarct evolution and the effect of therapeutic interventions.

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Limits of Reproducibility of Mitral Pulsed Doppler Spectra

JULES FAST, MD, INA VAN DAM, MD, ANCO HERINGA, MSc, THEO DE BOO, MSc, JOS ALSTERS, JEROEN HOPMAN, MSc, OTTO DANIELS, MD, and LAMBERT VAN DEN MERKHOF, MSc

The total intrinsic variability of pulsed Doppler spectra of mitral blood flow was evaluated in this study. Doppler examinations were performed in 10 normal volunteers (7 men, 3 women), ages 29 to 57 years (mean 41) with an interval period of 3 months. The recordings were made in the apical 4-chamber view, using a 2.25-MHz transducer. The sample was placed approximately 1 cm proximal (left atrium) and 1 cm distal (left ventricle) from the middle of the anulus of the mitral valve at the onset of diastole. Processing of the raw Doppler spectra was done in a way that avoided subjective manipulation by the investigators. Mitral peak velocities, accelerations and spectral widths were measured in early diastole and late diastole. From the parameters under investigation, maximal velocities showed the best reproducibility with a range of coefficients of variation of 9 to 13%. Peak acceleration in early diastole and spectral widths showed rather large coefficients of variation, ranging from 19 to 30 and 14 to 24%, respectively. Mitral pulsed Doppler spectra in the left atrium were more reproducible than in the left ventricle.

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Introduction of the single gated pulsed Doppler technique in echocardiography has significantly contributed to the assessment of mitral valve pathology[1] and Doppler evaluation of left ventricular diastolic filling.[2–4] Because it is noninvasive, Doppler 2-dimensional echocardiography is ideally suited for repetitive use to establish changes in mitral pulsed Doppler spectra (MPDS) as a consequence of either the natural evolution of a disease or a treatment. This application, however, is hampered by the uncertainty as to whether these changes observed in patients during serial studies carried out by the same or a different observer are real or artificial, caused by technical, physiological and interpretative sources of variability. Some inaccuracy relates to the way parameters are acquired from Doppler spectra, including X-Y tablets[5] and visual evaluation.[6,7] The present study was designed to determine the extent of variability in MPDS when a standardized way of measurement is used in a group of normal volunteers. Processing of the raw Doppler data was completely computerized in order to increase the reproducibility of our measurements.[8]

From the Departments of Cardiology, Pediatrics and Statistical Consultation, University of Nijmegen and Interuniversity Cardiology Institute, Utrecht, the Netherlands. Manuscript received August 28, 1987; revised manuscript received December 16, 1987, and accepted December 17.

Address for reprints: J.H. Fast, MD, Department of Cardiology, University Hospital Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands.

Methods

The ultrasonic examination was performed in 10 normal volunteers (7 men, 3 women), ages 27 to 58 years (mean 42). They were diagnosed as healthy by their checkup examinations, which included interviews, blood pressure measurement, cardiac auscultation, an electrocardiogram and 2-dimensional echocardiogram. The clinical condition did not change during the follow-up period of 3 months. The serial studies were carried out during normal respiration, at identical diurnal time points, after an interval of 2 to 3 hours following a light breakfast. The subjects were examined in the left lateral position after a short period of supine rest. The echo-Doppler examination was performed with a Honeywell Ultra-Imager using a frequency of 2.25 MHz. The recordings were made in the apical 4-chamber view. The sample volume with a length of approximately 5 mm was placed about 1 cm proximal (left atrium) and 1 cm distal (left ventricle) from the middle of the anulus of the mitral valve at the onset of diastole. The Doppler beam was angled in such a way that it was parallel to the assumed mitral

TABLE I The Mean and Standard Deviation as Parameters of Mitral Pulsed Doppler Spectra

Serial Studies	Study 1	Study 2	Study 3	Study 4
Left ventricle				
Vmax E (cm/s)	57 ± 12	64 ± 12	57 ± 10	56 ± 8
Width E (cm/s)	6.1 ± 1.4	6.3 ± 1.2	7.1 ± 2.1	8.1 ± 3.1
Amax E (cm/s^2)	1,150 ± 350	1,370 ± 310	1,130 ± 310	960 ± 280
Vmax A (cm/s)	38 ± 13	41 ± 10	37 ± 13	34 ± 8
Width A (cm/s)	7.3 ± 1.5	6.5 ± 1.3	7.4 ± 2.1	6.9 ± 2.8
E/A ratio	1.65 ± 0.47	1.63 ± 0.38	1.74 ± 0.59	1.80 ± 0.65
HR (beats/min)	74 ± 10	72 ± 10	73 ± 7	71 ± 7
Left atrium				
Vmax E (cm/s)	46 ± 8*	47 ± 7*	49 ± 8*	44 ± 10*
Width E (cm/s)	6.5 ± 1.7	6.8 ± 2.1	7.7 ± 1.7	8.0 ± 2.5
Amax E (cm/s^2)	710 ± 160*	670 ± 150*	750 ± 90*	610 ± 220*
Vmax A (cm/s)	36 ± 9	36 ± 10	35 ± 9	35 ± 9
Width A (cm/s)	6.6 ± 1.4	6.2 ± 1.5	6.7 ± 1.7	5.9 ± 2.2
E/A ratio	1.37 ± 0.49*	1.40 ± 0.55	1.51 ± 0.47	1.40 ± 0.56*
HR (beats/min)	75 ± 11	71 ± 11	71 ± 8	70 ± 6

Amax A = maximal acceleration of A wave; E/A ratio = ratio of peak E-wave velocity and peak A-wave velocity; HR = heart rate; Vmax E = maximal velocity of E wave.

* Significant difference between recordings in left ventricle and left atrium ($p < 0.05$).

TABLE II Coefficients of Variation

	Left Ventricle Studies				Left Atrium Studies			
	1–2	1–3	1–4	3–4	1–2	1–3	1–4	3–4
Vmax E	10	10	11	5	5	9	11	10
Width E	8	15	19	19	16	18	14	14
Amax E	20	16	30	27	8	13	19	21
Vmax A	11	14	13	12	6	10	9	8
Width A	17	19	24	28	19	13	18	15
E/A ratio	10	12	15	9	7	14	14	14

Abbreviations as in Table I.

valve flow. The direction of flow was assumed to be perpendicular to the plane of the mitral anulus. After 2-dimensional image positioning, the site of the sample volume was adjusted slightly in the third dimension based on the Doppler signal and echocardiographic verification. The device produced an amplitude spectrum with 100 points every 5 ms. The number of samples taken per second was 7,800 with a distance between transducer and sample of 6 to 10 cm and 4,875 with a distance of 10 to 16 cm. Depending on depth, time periods of spectral information were 100/7,800 s = 12.8 ms and 100/4,875 s = 20.5 ms, respectively. Hence, subsequent spectra were essentially not independent. The real-time amplitude spectra, together with adjustment data for the instrument (PRF, sample volume length and depth), were taken in digital form from the scanner with a Wicat computer offering a resolution of 12 bits. The spectrogram over 5 seconds (1,000 spectra) was stored. For further data processing, the data were transferred to a DEC PDP 11/44 minicomputer.

By squaring, the stored amplitude spectra were converted into power spectra, after correction for background noise, wall filter influence and transit time effects. The power over 3 successive spectra was averaged.

The lower quartile, median and upper quartile curves were computed from these smoothed spectra, considering each power spectrum as a velocity distribution.[8] For the characterization of the mitral blood flow, 4 parameters were calculated from the obtained curves: (1) the maximal median velocity in early diastole and in late diastole; (2) the ratio of peak E-wave velocity and peak A-wave velocity (E/A ratio); (3) the maximal acceleration during early diastole; (4) the dispersion of the velocity distribution around the maximal velocity in early and late diastole (width). The width was defined as the difference between the upper and lower quartile velocities.

For the analysis of each parameter, the median value of 3 successive heart beats was used. The recordings were made with an interval of 1 hour (numbers 1 and 2) and after 3 months (numbers 3 and 4). The recordings number 1, 2 and 3 were made by one and the same investigator and number 4 by another one. The time interval between the last 2 recordings was approximately half an hour. For each patient, the variability of the parameters was evaluated by the coefficients of variation, defined as the ratio of the standard deviation and the mean of 2 successive measurements, expressed in percentages. The coefficient of variation was averaged over all 10 patients.

The Wilcoxon signed rank test was used for evaluation of the presence of a systematic difference between 2 paired recordings. The level of significance was $p < 0.05$ in all tests.

Results

The parameters of MPDS for both left ventricle and left atrium are listed in Table I. All serial recordings with the sample volume located in the left atrium resulted in mean measurements significantly lower than those obtained at the level of the left ventricle inflow region for both peak velocities and accelarations in early diastole. The same was found for the E/A ratio in the recordings number 1 and 4. The coefficients of variation for each parameter are listed in Table II.

In general terms, the parameters in the left atrial outflow tract are more reproducible than those in the left ventricle's inflow region. Based on the analysis of the various parameters, the velocities showed the best reproducibility with a range of mean coefficients of variation from 5 to 14%. Peak acceleration and spectral width showed rather large coefficients of variation, ranging from 8 to 30 and from 8 to 28%, respectively. Reproducibility decreased as the time interval between the studies was prolonged from 1 hour (studies 1 and 2) to 3 months (studies 1 and 3). The sources of variability included the investigator as well. The coefficients of variation from studies 3 and 4 were larger than those from studies 1 and 2. The mean and standard deviation of the absolute differences between

TABLE III Mean and Standard Deviation of the Absolute Differences Between Paired Studies

Serial Studies	Studies 1–2	Studies 1–3	Studies 1–4	Studies 3–4
Left ventricle				
Vmax E (cm/s)	−6.4 ± 8.8*	0.4 ± 9.7	2.0 ± 10.7	2.4 ± 6.0
Width E (cm/s)	−0.2 ± 0.9	−1.1 ± 1.7	−1.9 ± 3.4	−0.7 ± 3.4
Amax E (cm/s^2)	−217 ± 290	23 ± 280	192 ± 530	205 ± 400
Vmax A (cm/s)	−2.9 ± 5.6	1.5 ± 8.7	5.6 ± 10.0	4.7 ± 8.7
Width A (cm/s)	0.8 ± 1.8	−0.1 ± 2.6	0.6 ± 3.1	0.8 ± 3.9
E/A ratio	0.02 ± 0.28	−0.09 ± 0.46	−0.19 ± 0.48	−0.14 ± 0.30
Left atrium				
Vmax E (cm/s)	−0.4 ± 4.4	−2.6 ± 7.5	2.2 ± 8.2	4.9 ± 8.7
Width E (cm/s)	−0.2 ± 1.9	−1.2 ± 2.1	−1.4 ± 2.2*	−0.2 ± 2.3
Amax E (cm/s^2)	38 ± 87	−19 ± 177	97 ± 176	116 ± 197
Vmax A (cm/s)	−0.2 ± 3.5	1.4 ± 6.1	1.3 ± 5.5	−0.1 ± 4.6
Width A (cm/s)	0.4 ± 1.8	−0.1 ± 1.8	0.7 ± 2.4	0.8 ± 1.8
E/A ratio	−0.03 ± 0.17	−0.14 ± 0.30	−0.03 ± 0.36	0.11 ± 0.37

Data are mean ± standard deviation.
Abbreviations as in Table I.
* Significant difference between paired measurements ($p < 0.05$).

paired recordings are listed in Table III. In general, no significant difference was found between paired measurements. In studies 1 and 4, the sign of the mean of the differences was equal on both sides of the mitral valve, indicating a consistent difference. A significant change was found only for both spectral width in the left atrium and peak velocity in the left ventricle in early diastole. The absolute differences, however, were rather small.

Discussion

The sequential reproducibility of Doppler parameters is determined by the interplay of many different factors. Crucial at the time of recording is the orientation of the ultrasound beam relative to the mitral blood flow, which should be as identical as possible in repetitive studies. Interception angles measured at the mitral orifice have been reported to be close to 0°, show minimal variability and be highly reproducible.[5] MPDS depend on the spatial position of the sample in the heart[7] and its corresponding volume, the motion of the heart[9] and the instantaneous velocity profiles in the left atrium and left ventricle.[10] In our study the sample was placed on both sides of the mitral valve, a position that should be as identical as possible in repeated studies. The heart, being a 3-dimensional structure, is nevertheless only visualized in a 2-dimensional image. Variability in sample position during serial studies may occur because the third dimension is not known. In a pilot study of 5 healthy subjects we found the anulus of the mitral valve to move 0.6 to 1.1 cm away from the apex at the end of expiration during diastole. With normal respiration, an additional shift of 0.7 to 1.3 cm to the right was seen during inspiration. As opposed to the anulus, the sample remains in a fixed position with reference to the transducer during diastole. The distance between the sample in the left ventricular inflow region and the anulus of the mitral valve may increase and the distance between the sample in the left atrial outflow region and the anulus may decrease during diastole. The consequences of such a displacement of the sample for MPDS greatly depend on the velocity profiles near the mitral valve orifice.

At the level of the left ventricular inflow region the profile is nonaxisymmetric, with much more rapid velocities occurring anteriorly than posteriorly.[10] With the assumption of a flat blood velocity profile in the mitral orifice,[10] the better reproducibility of Doppler measurements in the left atrium may be explained by the movement of the mitral anulus toward the sample in the left atrium during diastole. If paired sample volumes are not placed identically in serial studies, the extent of MPDS variability may be reduced in the presence of a velocity profile, which tends to flatten as blood converges from the left atrium to the mitral anulus. In the pilot study, 1 respiratory cycle included 5 to 7 cardiac cycles, depending on the heart rate. The use of a single arbitrary cycle, or even the average of a sequence of 3 cardiac cycles as in our study, while respiratory changes are disregarded, may increase the variability of MPDS in serial studies. However, in a previous study of 215 healthy subjects, ages 1 to 65 years, no influence of respiration on the ratio of peak E-wave velocity and peak A-wave velocity was found.[3]

With the Honeywell equipment (a mechanical echo-Doppler scanner), simultaneous 2-dimensional echo imaging and Doppler evaluation were not possible, creating some uncertainty as to whether the displacement of the sample itself during the Doppler study might have contributed to the variability of MPDS.

In clinical practice, the variability of MPDS may be even greater than in our study. A Doppler echocardiograph has a number of adjustment possibilities. Some of these affect the signals as stored by the computer, whereas other settings control the display only. Because the choice of a specific setting is subjective, the

strength of the present study is the completely computerized processing of the raw Doppler data.

In conclusion, our equipment made possible Doppler measurements of MPDS with acceptable interobserver and day-to-day variability for mitral peak velocities and the ratio of peak E- and A-wave velocities only. Except for the ratio, there is a need for standardization of respiratory phases in the assessment of MPDS.

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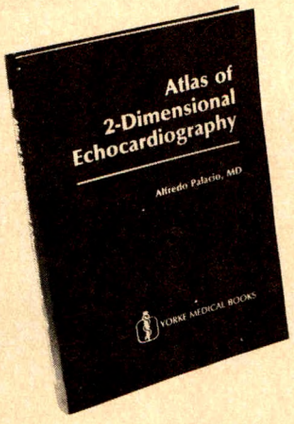

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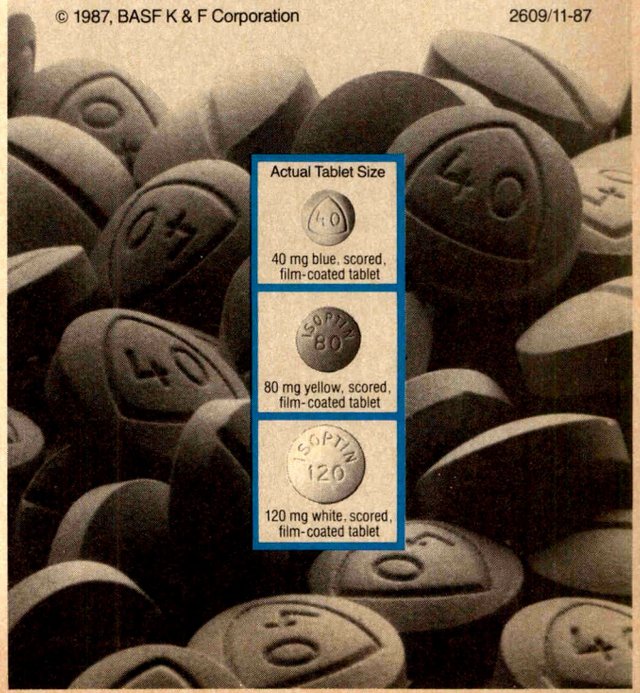

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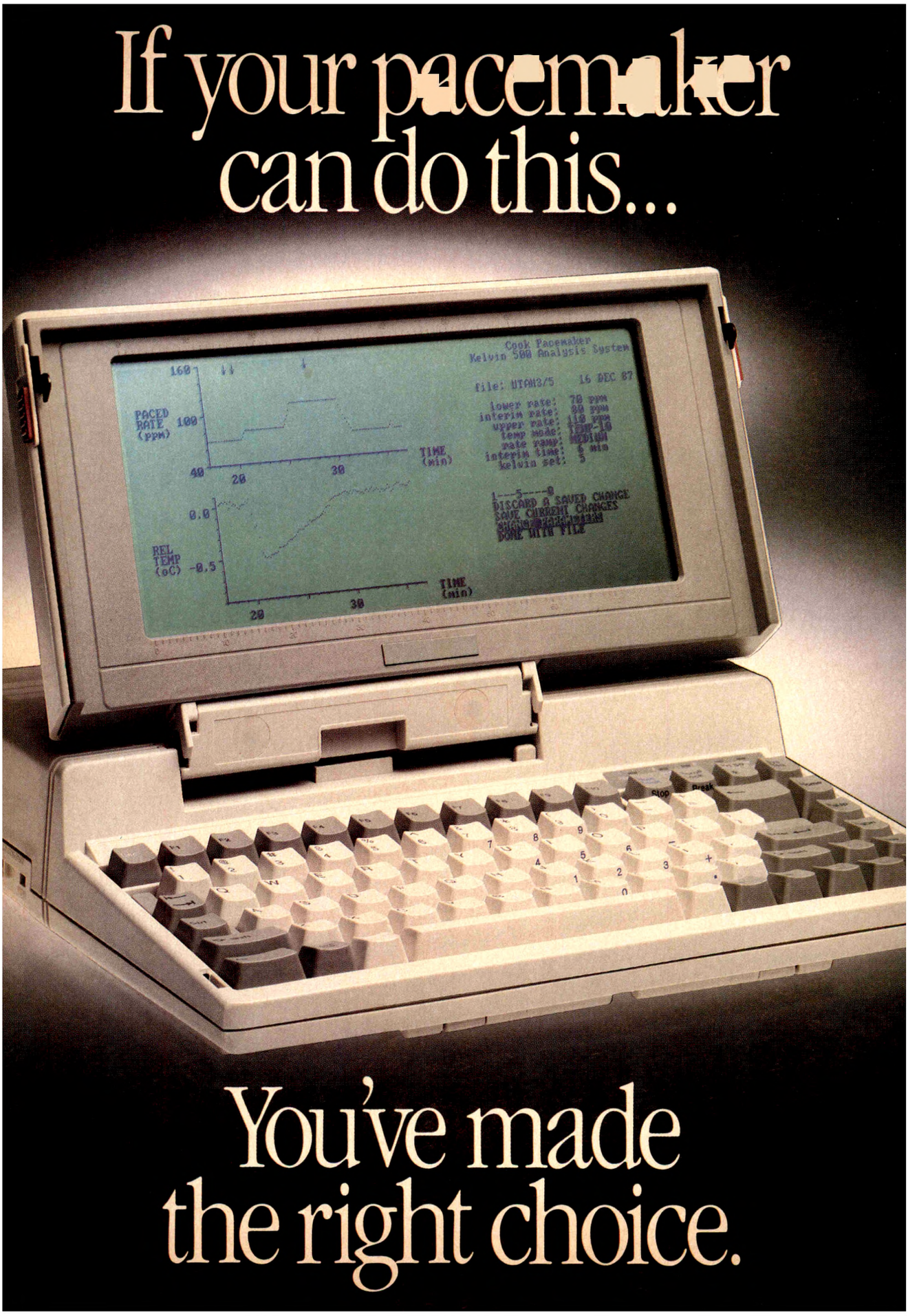

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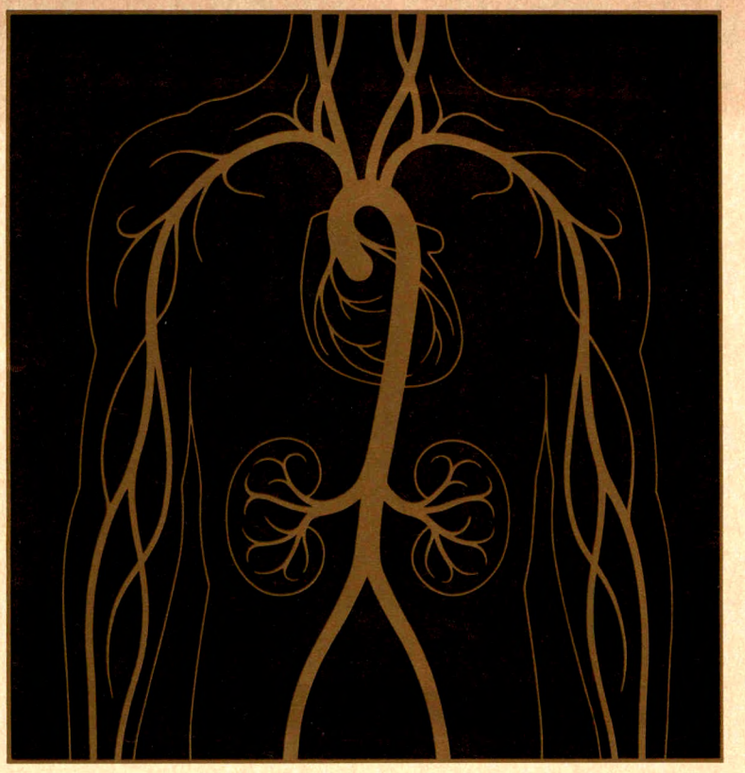

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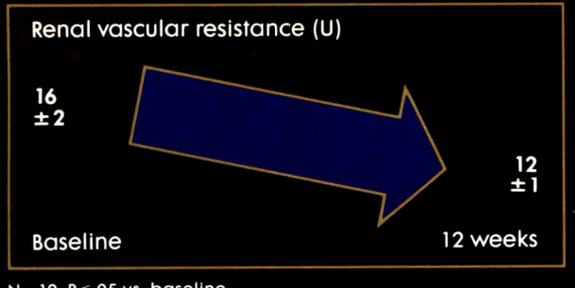

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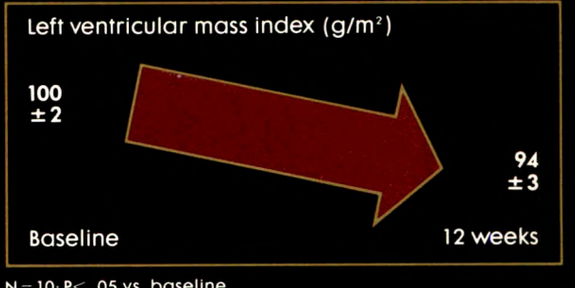

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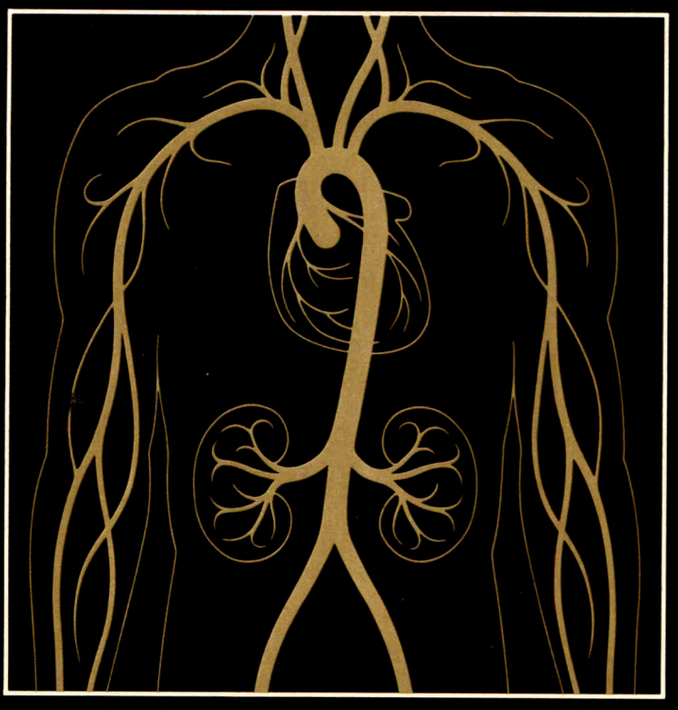

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From Irritable Heart to Mitral Valve Prolapse: World War I—The U.S. Experience and the Prevalence of Apical Systolic Murmurs and Mitral Regurgitation in Drafted Men Compared with Present Day Mitral Valve Prolapse Studies

CHARLES F. WOOLEY, MD, and HARISIOS BOUDOULAS, MD

The prevalence and recognition of disease have changed with time. During the present century in this country, rheumatic heart disease and coronary artery disease are examples of changing prevalence, whereas mitral valve prolapse (MVP) exemplifies changing recognition.

Whether the prevalence of MVP, presently recognized as a common form of valvular heart disease, has changed during this century is not known. In an attempt to address this question we reviewed U.S. military World War I physical examination data, specifically, the incidence of mitral regurgitation (MR) and apical systolic murmurs in 2.5 million young men examined for military service. We compared these data with the prevalence of MVP in U.S. men documented during the past decade.

World War I Examinations

Following the U.S. declaration of war in April 1917, the Selective Service Act, approved in May 1917, provided for registration of all men 21 to 30 years of age inclusive, setting the stage for the physical examination of almost 4 million men. The 1910 U.S. Army publication *Rules for Examination of Recruits* was revised and replaced with *Physical Examination Standards No. 1* in July 1917. Further clarification and simplification of diagnostic terminology and physical examination techniques and standards prompted 6 revisions, intended for the use of medical officers at recruiting stations, camps and cantonments, working with local or district boards or participating on medical advisory boards.

> The physical examinations were made by about 4,648 local boards, with more than that number of examining physicians. Many of the men were examined also by medical advisory boards, with a total number of 9,577 examining physicians. In addition, they were examined by thousands of medical officers at the numerous Army cantonments, camps, and posts.[1]

After the war, in 1920, the U.S. War Department published the 1,663-page document *Defects Found in Drafted Men*[1] (Figure 1), which contained statistical information compiled from the World War I draft records. Rarely referred to, the study included data on physical defects and diseases found in a half million men rejected by medical examiners of local boards and 2 million men examined at mobilization camps during the draft in 1917 and 1918, ages 18 to 30 inclusive. Data from the examination of 2,510,591 men were presented in the report.

The Cardiac Examination Criteria for Medical Officers

The criteria for cardiovascular examination were quite specific:

> Normal heart. A heart shall be considered normal when the apex impulse is within the left nipple line

From the Division of Cardiology, College of Medicine, The Ohio State University, Columbus, Ohio. This study was supported by the Overstreet Cardiovascular Teaching and Research Laboratory, Division of Cardiology, College of Medicine, The Ohio State University, and The Columbus Foundation, Columbus, Ohio. Manuscript received September 2, 1987; revised manuscript received and accepted December 10, 1987.

Address for reprints: Charles F. Wooley, MD, University Hospitals, Room 647, Means Hall, 1654 Upham Drive, Columbus, Ohio 43210.

and not below the fifth interspace, not heaving in character, with normal sounds, free from murmurs, absence of pulsation or dullness above the base of the heart, regular pulse of normal rate, no unusual thickening of the arteries or evidence of high blood pressure, and a normal response to the exercise test. . .The following defects shall be unconditionally rejected for all military service: a) Circulatory failure evidenced by definite symptoms such as a combination of breathlessness, marked cyanosis or edema, b) Hypertrophy and dilation of the heart evidenced by displacement of the apex impulse to the left of the nipple line or below the sixth rib, and of a heaving or diffuse character, c) Valvular disease, as evidenced by characteristic murmurs, enlargement of the heart, and a lack of the normal response to exercise. When Local Boards are in doubt concerning the physical fitness of registrants who suffer from defects due to conditions of the heart or blood vessels, they shall refer them to the Medical Advisory Boards.

Specific principles for interpretation of symptoms and signs referable to the heart were presented:

. . .given a heart of normal size and responding normally to effort, any murmur that is heard should be considered accidental and insignificant unless it can be positively demonstrated that it is a mitral or aortic diastolic murmur. . .Systolic murmurs unassociated with enlargement of the heart, alteration of the first sound, accentuation of the pulmonic second sound, or abnormal response to exercise may also be considered as without significance. Loud systolic murmurs, audible at the apex and in the left back, if associated with any enlargement of the heart, with snapping first sound, or accentuation of the pulmonic second sound, constitute a disqualifying defect.

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Prepared under the direction of
The Surgeon General, M. W. IRELAND
Major General, M. C., U. S. Army

By

ALBERT G. LOVE, M. D.
Major, M. C., U. S. Army
and
CHARLES B. DAVENPORT
Formerly Major, S. C., U. S. Army

WASHINGTON
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FIGURE 1. Front page from the 1920 report released by the War Department.[1]

Results

Defects were found in approximately one-half of the men (Table I). Valvular heart disease was found in 85,143 (3.39% of the total 2,510,591 men examined). The incidence in each category of valvular disease is summarized in Table II. For reasons not stated, 44,143 of these men were not further classified, but, of the 40,330 men who were, 29,610 (73.4%) had MR. Assuming that the incidence of valvular disease was the same in the entire population, the *estimated percent incidence* of each valvular heart disease can be calculated (Table III).

Cardiovascular Examination of Recruits at the Camps During World War I

Special cardiovascular examinations were performed in many areas. The incidence of apical systolic murmurs in 3 different regions of the country comes from the following sources.

Texas: The cardiovascular board at Camp Travis, Fort Sam Houston, Texas, examined 55,000 men from Texas and Oklahoma 21 to 31 years of age.[2] Fifty men had aortic insufficiency (0.09%) and a lower incidence of mitral stenosis (0.02%), idiopathic hypertrophy (0.01%) and systemic hypertension (0.02%). "Accidental" systolic murmurs at the apex were found in 3.2%; because these were considered of no significance unless accompanied by signs of hypertrophy, only 39 men were diagnosed as having isolated MR (0.07%).

Washington: Special cardiovascular examinations were performed on every recruit at Camp Lewis, Washington, by a board that included 3 permanent cardiovascular examiners.[3] Although MR was diagnosed in 1,176 of the total 30,697 men examined (5.6%), only 418 were rejected. The large number of men with MR had the characteristic murmurs, but because there was no cardiac hypertrophy and no history of acute rheumatic fever or chorea, they were accepted for full duty.

New York: Marcus Rothschild, 1 of the 6 U.S. Army medical officers assigned earlier to the British "Heart Hospital," participated in the preparation of the U.S. medical officers' *Report on Neurocirculatory Asthenia*[4] and later discussed the diagnosis of MR based upon his experience at the Syracuse Recruit Camp.[5]

Systolic murmurs were recorded in 870 men (8.7%) in a group of 10,000 men accepted for limited service. When the criteria of cardiac hypertrophy, apical sys-

tolic murmur and history of articular rheumatism were used as the basis for the diagnosis of MR rather than the murmur alone, the diagnosis was limited to 33 cases (0.33%) of the total examined. Rothschild explained the dilemma:

> It must be admitted that, given a soldier with no hypertrophy, no definite history of acute articular rheumatism and no symptoms, but with a *loud, musical, systolic murmur at the apex transmitted to the axilla* and angle of the scapula, because of one's previous training and habit of thought, *it is extremely difficult to disregard this murmur absolutely*. (Emphasis added.) The plea is made, however, not to lay too much emphasis on this murmur. . .
>
> The differential diagnosis of mitral valvulitis (regurgitation) must be made from the following conditions: 1) functional cardiovascular disorder, disordered action of the heart, 'irritable heart of soldiers', neurocirculatory asthenia; 2) accidental systolic, apical murmurs. . .The ruling of Lewis (Thomas Lewis) on apical systolic murmurs is, to my mind, sound. *The systolic murmur per se is disregarded.* The soldier is disqualified because of a poor exercise response, not because of a systolic murmur; or his service is limited because of a definite attack of rheumatic fever, and not because of a systolic murmur.

The 1918 Perspective

The data from the massive report *Defects Found in Drafted Men* and the reports from the individual camps presented a repetitive theme. The majority of young men with the diagnosis of valvular heart disease were classified as isolated MR. That some of these young men with apical systolic murmurs were the precursors of the patients with MVP, as defined later in the twentieth century, seems reasonable in retrospect.

A. E. Cohn, then a major in the U.S. Army and senior consultant in general medicine in the American Expeditionary Force, discussed the basic questions. What was the significance of apical systolic murmurs, especially their relation to MR? This had been a subject of debate for at least a half a century. In addition, should these men be accepted for military service? Cohn expressed concern that reliable guides for decision-making were wanting.[6] He shared Rothschild's concerns and realized that new criteria were necessary to decide which types of systolic murmur were important and which were not. Most of the revised diagnostic criteria were other than auscultatory, i.e., heart size, history of rheumatism, intensity of the second heart sound and pulse rate response to exertion.

The 1918 experience involved the physical examination of approximately 4 million young men. Physicians developed, modified or standardized diagnostic and classification criteria where few had previously existed. Clinical judgments were based on conventional wisdom, however, for the matter of fitness for military service took precedence.

The impressive summary document *Defects Found in Drafted Men* reflected the massive effort that produced clinical epidemiologic classifications and tabulations of diseases and defects, based upon the examination of 4 million young men across the entire nation. This may have been the first published "medical census" in modern medicine.

TABLE I Common Defects in Drafted Men

Defect	%
Mechanical (bones, joints, hands, feet)	39
Sense organs (vision, hearing)	12
Tuberculosis and venereal diseases	11
Cardiovascular diseases	10
Development—metabolic diseases	10
Nervous—mental diseases	6

TABLE II Valvular Disease in Drafted Men (Classification of 40,330 Men)

	Pts (n)	%
Mitral regurgitation	29,610	73.4
Mitral stenosis	7,469	18.5
Aortic regurgitation	3,658	9.0
Aortic stenosis	1,263	3.1
Aortic and mitral lesions	1,184	2.9

TABLE III Valvular Disease in Drafted Men (Estimated Frequency in 2,510,559 Men)

Valvular Disease	%
Total valvular disease	3.39
Mitral regurgitation	2.48
Mitral stenosis	0.63
Aortic regurgitation	0.31
Aortic stenosis	0.11
Aortic and mitral lesions	0.10

Mitral Valve Prolapse and the 1980 Perspective

The prevalence of MVP is uncertain. Published figures reflect differences in selection, investigative techniques, diagnostic criteria and populations. Data comparing the incidence of MVP in different ethnic groups are limited, current diagnostic techniques have intrinsic limitations and there may be significant day-to-day variations in cardiac auscultatory findings in certain individuals. Phonocardiographic confirmation of the auscultatory findings, a valuable adjunct to auscultation, was not obtained in several of the epidemiologic studies. Evolving echocardiographic MVP criteria have been revised with the development of newer imaging techniques, and auscultatory—echocardiographic correlations are limited. Necropsy studies contribute to MVP natural history studies but involve older populations which do not necessarily reflect the incidence of MVP in the younger population. However, comparison of 1917–1918 MR data with current MVP epidemiologic studies may be relevant to the irritable heart-MVP story.

TABLE IV Prevalence of Mitral Valve Prolapse

Author	Year of Publication	Population	Pts (n)	Method	MVP (%) in Males
Bloch et al[7]	1977	U.S. Boston volunteers	73	Echo	4.1
Valdez et al[8]	1979	U.S. Stanford employees	105	Echo	4.7
Lucas et al[10]	1982	U.S.	750	Necropsy	8.3
Savage et al[13]	1981	U.S. Framingham	4976	Echo	2–4*
Greenwood[11]	1984	U.S. children	3100	Auscultatory	4.97
Greenwood[12]	1986	U.S. children	6168	Auscultatory	5.37
Khandheria et al[9]	1987	U.S.	2264	2-dimensional echo	11.6

* See also Figure 2.
MVP = mitral valve prolapse.

Results

The prevalence of MVP in men reported in the U.S. from different investigators using echocardiographic studies varied from 4.1 to 11.6%.[7–9] The incidence of floppy valves in 1 necropsy study was 8.3%,[10] whereas the incidence of MVP in auscultatory studies ranged from 4.97 to 5.37%[11,12] (Table IV).

Echocardiographic MVP was detected in 5% of the total 4,967 subjects in the Framingham study. The prevalence of MVP in the male population was reasonably consistent at 2 to 4% from those between ages 20 and 30 through those who were 80 to 90 years old[13] (Figure 2).

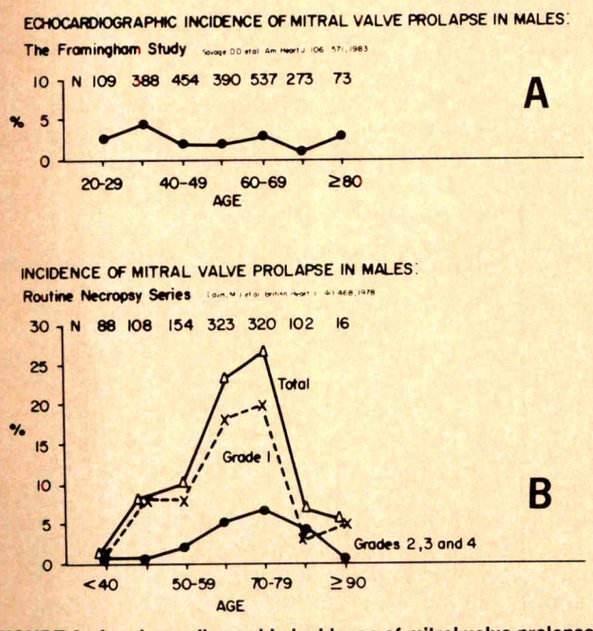

FIGURE 2. *A*, echocardiographic incidence of mitral valve prolapse (MVP) in males from the Framingham Study (modified from Savage DD et al[13]). *B*, incidence of MVP in males from a prospective necropsy study. Grade 1 = mild, grade 2 = moderate, grade 3 = moderately severe and grade 4 = severe floppiness of mitral valve (MVP). The total represents all patients with grades 1, 2, 3 and 4 (data from Davies MJ et al[14]). From Boudoulas H, Wooley CF.[19]

Davies et al[14] reported that the overall prevalence of MVP (floppy mitral valves) was 4% in men in 1,111 routine necropsies performed in men in 4 London general hospitals. The severity of prolapse was graded as 0 (none), grade 1 (minimal involvement), grade 2 (extensive prolapse of 1 or both cusps), grade 3 (chordal rupture) and grade 4 (chordal fusion to ventricular wall). MR was attributed only to grade 2 to grade 4 valves, which were called "floppy mitral valves" (Figure 2).[14]

The incidence of apical systolic murmurs in patients with MVP varies from study to study; in the younger population, systolic murmurs have been reported in <50% of patients with echocardiographic MVP. Thus, it appears that the reported contemporary incidence of apical systolic murmurs in males 20 to 40 years of age may approximate 2 to 3%.

Summing up: During the U.S. experience in World War I, approximately 4 million young men were examined. The incidence of cardiovascular defects was appreciable. MR was the most frequent valve lesion and far exceeded all other valve lesions, individual or combined. The repetitive theme, that MR is a common phenomenon, extends from World War I to the 1980s and has gained new clinical importance as we learn more about the natural history of MVP,[15] MR[16] and cardiovascular disorders of connective tissue origin.[17]

We conclude that the prevalence of apical systolic murmurs and the diagnosis of MR in young Americans during World War I parallels the prevalence of apical systolic murmurs and MVP among young men in the 1980s.

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Lewis A. Conner, MD (1867–1950), and Lessons Learned from Examining Four Million Young Men in World War I

CHARLES F. WOOLEY, MD

The physical examination process of the U.S. Army during World War I involved almost 4 million young men. It required the U.S. Army to update the 1910 version of its *Rules for Examination of Recruits* and to revise and clarify cardiovascular physical examination standards and terminology.[1]

The definition, differential diagnosis and disposition of young men with irritable heart, soldier's heart and mitral regurgitation had been an early and major military medical problem in England during World War I. The consequences in terms of fitness for duty, military time loss and cost of disability, rehabilitation and pensions were enormous and unexpected.[2] The same concern, confusion and debate over cardiovascular diagnosis occurring in England[3–5] ultimately affected the U.S. Large numbers of asymptomatic young men with apical systolic murmurs without cardiomegaly posed diagnostic and disposition problems for examining physicians. Another large group of young men with a constellation of disabling cardiovascular symptoms, with or without apical systolic murmurs, required decisions about fitness for military service.

Lewis A. Conner took " . . . stock of what has been accomplished by all this elaborate effort" in the U.S. when he presented "Cardiac Diagnosis in the Light of Experiences with Army Physical Examinations" at the Association of American Physicians' meeting in Atlantic City in June 1919.[6] The present article reviews Conner's observations on cardiac diagnosis during the wartime physical examination process instituted in the U.S. Army. A brief sketch of his medical and cardiological experience in the U.S. is presented as a background to this link from irritable heart to mitral valve prolapse.

From the Division of Cardiology, College of Medicine, The Ohio State University, Columbus, Ohio. This study was supported by the Overstreet Cardiovascular Teaching and Research Laboratory, Division of Cardiology, College of Medicine, The Ohio State University, and The Columbus Foundation, Columbus, Ohio. Manuscript received September 30, 1987; revised manuscript received December 23, 1987, and accepted December 28.

Address for reprints: Charles F. Wooley, MD, University Hospitals, Room 647, Means Hall, 1654 Upham Drive, Columbus, Ohio 43210.

Lessons Learned

During the 19 months between the U.S. entrance into the war and the Armistice, approximately 4 million young men were "subjected to a special physical examination of their circulatory apparatus by officers chosen for their supposed special fitness for this work." Conner presented the lessons learned under several distinct categories:

The lessons learned about cardiac diagnosis: Simply put, standardized methods of examination and criteria for diagnosis of large numbers of normal young men had never been implemented before in the U.S.

"No similar examinations upon any such gigantic scale have ever before been attempted. . .a real advance has been made in certain phases of cardiac diagnosis. . .chiefly through the opportunity afforded to examine an immense number of young men, almost all of whom were normal subjects, and to learn the frequency and the extent of normal variations of the physical signs of the heart."

Just how to define and classify apical systolic murmurs concerned Conner. "Accidental murmurs. . . even under the most rigid interpretation of the term the occurrence of such systolic accidental or functional murmurs is surprisingly frequent. . .such apical accidental murmurs are very common. It is not possible to give accurate statistics, but I am convinced, in the light of my own experience, that it would be conservative to say that at least nine-tenths of all *apical systolic murmurs in young adults belong to the class of accidental or functional murmurs.* (Emphasis added.)

These apical systolic accidental murmurs have several features. . .their inconstancy. They may be absent during rest and be pronounced after exercise or during excitement. The first sound may be quite clear and normal in the erect posture and have all the character-

istics of a murmur in the recumbent position. . .they usually show no tendency to be transmitted to the left of the apex; then, too, the murmur is obviously only the modified and changed first sound; it is not something clearly distinct from and additional to the heart sound as is so commonly the case with the murmur of mitral insufficiency. Lastly, such accidental murmurs seem rarely if ever to have the peculiar high-pitched, whizzing or blowing quality usually possessed by those due to mitral insufficiency."[6]

The lessons learned about functional disorders of the heart: "The irritable heart of soldiers (The Effort Syndrome, Neurocirculatory Asthenia). . .was far away the commonest disorder encountered and transcended in interest and importance all the other heart affections combined." Conner reviewed the conventional wisdom about "Soldier's Heart" almost verbatim from a report on neurocirculatory asthenia and its management[7] written by the U.S. medical officers detailed to the British Heart Hospital in England, which in turn incorporated the "Soldier's Heart" experience[8] with only the name changed. He emphasized the difficulties in separating " . . . 'soldier's heart' and 'effort syndrome' from valvular heart disease, particularly mitral insufficiency. . .the great danger, even with experienced examiners, of mistaking this neurosis for some organic disease of the heart. . .It was indeed often difficult to believe that a soldier who, on even moderate exertion, showed an array of striking symptoms (dyspnea, exhaustion, precordial pain, tremulousness, cyanosis, extreme tachycardia) could be suffering merely from a neurosis. Moreover, certain of the physical signs sometimes bore a close resemblance to those of mitral insufficiency. . .The pronounced and widespread cardiac impulse often suggested cardiac enlargement; the first sound at the apex was usually extremely short and sharp and the second pulmonic sound often very loud; a systolic accidental murmur was sometimes present and the suggestion of a thrill was often given to the palpating hand in the apical region. . .Thus with such a combination of pronounced symptoms and suggestive physical signs it is not surprising that a good deal of time was needed to educate the great body of medical officers to the true nature of these cases."[6]

The lessons learned about mitral regurgitation: Conner addressed the differential diagnosis of mitral regurgitation as follows. "The Effort Syndrome was the condition most frequently mistaken for mitral insufficiency. . .The rapid and violent heart action and pronounced cardiac impulse frequently gave the impression of cardiac hypertrophy; if, in addition, there was to be heard an apical accidental murmur the resemblance to mitral insufficiency might be close and, to the uninitiated, the diagnosis would seem to be confirmed by the pronounced subjective symptoms of precordial pain, dyspnea, palpitation, etc. With increasing experience in the recognition of the effort syndrome its confusion with mitral insufficiency became less and less frequent, for the two conditions bear little real resemblance to each other. The tachycardia, which is so constant and marked a feature of the 'soldiers' heart' is no part of the clinical picture of mitral leakage, and, as has been said, the pronounced subjective symptoms were characteristic of the neurosis and were altogether lacking in the valvular cases.

The question has been much discussed of late as to whether one is ever justified in making a positive diagnosis of mitral insufficiency on the existence of an apical murmur alone, and in the absence of signs of hypertrophy and of a history of definite attacks of rheumatic fever, even though the murmur have those special characteristics of transmission and quality which are supposed to belong to that disease. My own attitude toward this question has been modified a good deal by my army experiences and without venturing to be dogmatic upon the subject I am inclined to believe that *one will make fewest mistakes in the diagnosis of mitral regurgitation by adhering to the rule of never venturing a diagnosis on the presence of a murmur alone, no matter how characteristic it may seem to be.* (Emphasis added.) It is certain that if this rule were generally followed, uncomplicated mitral insufficiency would take its place among the less frequent forms of valvular disease, as I believe it deserves to do."[6]

Conner illustrated this point with Rothschild's[9] analysis of the records of 10,000 recruits accepted for

FIGURE 1. Lewis A. Conner (1867–1950). Courtesy of the National Library of Medicine, National Institutes of Health.

limited service. Although 870 had apical systolic murmurs, when the criteria for the diagnosis of mitral regurgitation were modified from murmur alone to the combination of murmur, cardiac hypertrophy and a definite history of rheumatic fever, then only 33(3.8%) fulfilled these criteria for the diagnosis of mitral regurgitation.

The lessons learned about common types of heart disease seen by hospital physicians in civil life: Conner found that degenerative conditions common to middle and old age, severe forms and advanced stages of rheumatic valvular disease and syphilitic disease of the aorta and heart "were conspicuous by their rarity."

Lewis A. Conner (1867–1950)

Conner was one of the founders and the first president (1924–1925) of the American Heart Association; a major memorial lecture at the annual meeting bears his name. He was also the first editor-in-chief of *The American Heart Journal*, the original periodical of this association, from 1925 until 1937.

He wrote sparingly and left only a modest tangible legacy. His bequest took a different form. David Barr[10] recalled that his "preeminence as a teacher can be attested by all graduates of Cornell who came into . . .contact with his remarkable example and method. His learning, his clinical judgment, and above all his integrity, made him the idol of the students and particularly of those chosen young men who were permitted to work with him as interns or residents in the wards of the New York Hospital."

Conner was born in Indiana, attended Yale University and the College of Physicians and Surgeons of Columbia University. He received his MD degree in 1890 and was appointed as house officer at New York Hospital in January 1892.[10] Later, he served as a private in the Spanish-American War. A member of the original faculty of Cornell University Medical College in 1898, he was appointed professor of clinical medicine at the age of 34 and eventually succeeded W. Gilman Thompson as professor of medicine in 1916. All of his professional lifetime was devoted to the New York Hospital and Cornell University Medical College. During World War I he was a colonel in the U.S. Army Medical Corps.

Dickson W. Richards, in the 1953 Conner Memorial Lecture, commented ". . .he was throughout his long life primarily a clinician and a teacher of medicine. . .a master in the art and science of physical diagnosis . . .held firm to the belief that new advances should support and add to our simpler forms of knowledge, rather than replace them; that in the analysis and treatment of disease, laboratory findings, whatever their nature should be our servants and not our masters."[11]

J. James Smith[12] touched the legend and tells us about the man. "Educated at a time when the unaided senses still represented the only resource in the clinical study and recognition of many diseases, Dr. Conner's mastery of physical diagnosis must have frequently astonished the uninitiated house officer."

One such young physician, while presenting a case of lung abscess following pneumococcal pneumonia at Grand Rounds, reported incredulously that the correct diagnosis had been made at the Burke Convalescent Home by a very aged physician who didn't even have a stethoscope. This man had never seen Dr. Conner palpate for the cardiac apex with his gnarled fingers, after which he announced a "high degree of mitral stenosis." This was before he listened, which of course was with sounding towel and naked ear, for his hearing loss largely defeated the use of the stethoscope."

Smith also recounted the lumbar puncture vignette: "One of the few details about his career that Dr. Conner ever told me personally was said hesitatingly, almost sheepishly. He said he thought he had performed the first lumbar puncture on a living man on this Continent. . .

It seems that during a tour of Europe in the 1890s, which in those days was an important finishing-off process in medical education, he had visited the clinic in Kiel of Heinrich Quincke, who was then developing the technique of lumbar puncture. Quincke describes this in 2 papers published in *Berlin Klinische Wochenschrift*, 28, 929, 1891 and 32, 889, 1895. In the latter paper he reports that the needles were fabricated for him by 'instrumentenmacher Assman.' With rare foresight, apparently well aware of the importance of the technique, Lewis Conner brought a supply of these needles back with him. . .

It was in the House of Relief, probably in the reception ward, where Lewis Conner performed the lumbar puncture with his German-made needle. His introduction of this technique could not have been more timely [as]. . .epidemic meningitis was an important disease at the turn of the century."[12]

Perspective

While there are limitations in looking back and analyzing time-distorted experience, there are lessons to be learned.

The U.S. "Grand Experiment" during World War I, when 4,000,000 young men were examined in an organized, systematic manner was a new medical experience in this country. Physical defects were found in approximately one-half of the men examined.[13] Cardiovascular defects were discovered in approximately 5% of the men examined, the majority of which were classified as valvular heart disease. Of those within the group with valvular heart disease that were further classified by defect, 65% were classified as mitral insufficiency.[1,13] Another large group was classified under the title of functional heart disease, cardiac arrhythmias or persistent tachycardia.

Reviewing the Conner article[6] and the massive document *Defects Found in Drafted Men*[1] helps us to understand how the examiners interpreted the physical diagnostic criteria in the military setting and the difficulties they had in the differential diagnosis of irritable heart, effort syndrome, neurocirculatory asthenia and mild mitral regurgitation. Even the veteran clinicians were dealing with phenomena new to their experience.

The textbooks of the day described patients with well-established or far advanced valvular heart dis-

ease and the descriptions of patients with mitral regurgitations reflected this bias. The cardiovascular phenomena in young men that the physical examination process uncovered during World War I required a modification of the conventional wisdom.

Conner's conclusion that nine-tenths of all apical systolic murmurs were accidental or functional echoed the precepts of the early French auscultors[14] and the then current British dogma articulated by Mackenzie[3] and Lewis[5] from the "soldier's heart" and "Heart Hospital" experiences. Although Clifford Allbutt[4] presented a dissenting voice to those concepts in England as also did earlier American clinicians such as Griffith, Hall and Prince, these minority opinions were buried by the more authoritative views.[14]

When physicians serve masters other than their patients, the results are frequently difficult to understand in medical terms. The British insurance-government-military complex of those years supported the British "Heart Hospital" research but had the needs of the military service and the cost of prolonged hospital stays, rehabilitation and pensions as primary concerns.[2] A war that left 9 million dead and 22 million wounded required, while it raged, endless numbers of bodies for sacrifice and was not an ideal environment in which to attempt to resolve these cardiac diagnostic dilemmas.

Although the physical examination process instituted during World War I had a positive impact on the development of cardiovascular physical diagnostic criteria and standardization of terminology in the U.S., the authoritative, summary dismissal of apical systolic murmurs as diagnostic criteria for mitral insufficiency served to impede curiosity, retard original thought and limit natural history studies for another 4 decades.

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Low Dose Aspirin After Early Thrombolysis in Anterior Wall Acute Myocardial Infarction

FREEK W.A. VERHEUGT, MD
ALBERT J. FUNKE KÜPPER, MD
TJEBBE W. GALEMA, MD
JAN P. ROOS, MD

Early thrombolysis has become the standard treatment of patients who have transmural acute myocardial infarction (AMI) and has proven to be the most effective in anterior AMI in terms of survival and left ventricular function.[1-3] Reinfarction as a result of coronary reocclusion remains the major drawback of early thrombolysis and occurs mainly in the first 3 months after AMI.[2] Strategies to prevent reinfarction include coronary artery bypass surgery, coronary angioplasty and drug treatment. Randomized trials of surgery after thrombolysis are lacking and those involving coronary angioplasty have had negative results.[4,5] We present the results of a prospective, randomized, double-blind placebo-controlled trial of low dose aspirin after early thrombolysis in patients with first anterior wall AMI.

Patients were eligible for entry in the study if they had (1) early (<4 hours) symptoms and electrocardiographic signs of first anterior wall AMI (ST-segment elevation of >2 mm in the precordial leads in the absence of precordial Q waves), (2) no contraindication to thrombolytic therapy (age older than 70 years, bleeding tendency, recent cerebrovascular accident, menstruation, antithrombotic treatment or cardiac massage) and (3) no contraindication to aspirin (recent gastrointestinal ulcer). After treatment with 1,500,000 U streptokinase intravenously, the patients provided informed consent. Subsequently, they were randomized to receive 1 capsule a day containing 100 mg acetylsalicylic acid or placebo. The first capsule was given immediately after informed consent. Further antithrombotic treatment consisted of heparin 5,000 U subcutaneously twice a day until full mobilization occurred. Standard coronary care was given to all patients.[2] If not contraindicated, atenolol 100 mg daily was administered routinely. Calcium antagonists and nitrates were added only when needed. Special attention was given to the recurrence of ischemic events. Unstable angina pectoris was defined as the occurrence of anginal pain at rest or minimal physical activity with accompanying ST changes on electrocardiography and normal plasma levels of creatine kinase-MB 6 hours later. Reinfarction was diagnosed when anginal pain recurred together with ST changes or new Q waves or both, followed by a significant increase in creatine kinase-MB, creatine phosphokinase, serum glutamine oxalate transferase and lactic dehydrogenase (more than twice the upper normal level or the last level before the pain attack). Sequential 2-dimensional echocardiopgraphy was performed during the coronary care unit stay and left ventricular wall motion abnormalities were scored as described earlier.[6] Heart catheterization was intended for all patients within 6 weeks after admission and consisted of left ventricular angiography and coronary angiography. Left ventriculograms were taken in the right anterior oblique position and left ventricular end-diastolic volume and ejection fraction were calculated.[3] On coronary angiography the left anterior descending artery was regarded as occluded when the vessel was not visualized at all, showed retrograde filling by collateral vessels or anterograde filling, but not complete within 3 heart cycles (functionally occluded). The angiograms were interpreted by 2 experienced cardiologists. In case of equivocal results the view of a third cardiologist was decisive. After discharge the patients were followed up in the out-patient clinic. The study medication was withdrawn after 3 months.

Twenty-four patients received aspirin and 26 placebo. Relevant baseline characteristics are listed in Table I. No significant differences were observed. Three-month follow-up was complete in all patients and the occurrence of recurrent ischemic events, death and revascularization are listed in Table II. Reinfarction in the aspirin group was noted on day 3 and days 2, 3, 7, 11, 14 and 27 in the placebo group. Angiography was performed in 25 patients (50%) within 6 weeks after randomization. In the other pa-

From the Department of Cardiology, Free University Hospital, Interuniversity Cardiology Institute, Amsterdam, The Netherlands. This study was supported in part by a grant from the Dutch Heart Foundation. Manuscript received September 21, 1987; revised manuscript received December 3, 1987, and accepted December 4.

tients angiography was not performed because of death (2 in the aspirin group, 2 in placebo group), severe peripheral vascular disease (3 aspirin), brain embolism (1 aspirin) and refusal (9 aspirin, 8 placebo). The characteristics of patients who did and did not undergo angiography are listed in Table III. Except for age, there were no significant differences in clinical and hemodynamic parameters. Table IV shows the angiographic results. Bleeding complications as defined earlier[7] were not encountered in any patient, either in the acute phase of the AMI or during follow-up or heart catheterization.

Low dose aspirin (≤325 mg daily) has been shown to be effective in patients with unstable angina[8] and after coronary bypass surgery.[9] We report the effectiveness of the same regimen in the prevention of coronary reocclusin after early thrombolysis resulting in a lesser incidence of reinfarction and in better preservation of left ventricular function. This is in contrast with the negative outcome of earlier much larger studies on the effect of aspirin after AMI from the era before early thrombolytic therapy. These negative results might be due to the relatively low incidence of spontaneous early (<4 hours) coronary reperfusion, the dose of aspirin and the late patient inclusion in the earlier studies. However, our results correlate well with those of the recently published International Studies on Infarct Survival-2 on the efficacy of streptokinase, aspirin, heparin and placebo in AMI.[10] Although the design of the latter study lacks angiography and is much more complex and different, the clinical outcome in our patients treated with streptokinase and aspirin is similar in terms of reinfarction.

Unlike in inferior wall AMI, in anterior wall AMI the infarct-related coronary artery can be identified beyond doubt, which makes the angiographic design of our study reliable and simple. On the other hand, many of the angiographic data are lacking due to death or refusal. Therefore, our angiographic results should be interpreted with care. Special attention must be paid to the relatively high rate of occlusion of the left anterior descending coronary artery in the placebo-treated group. It is unlikely that this finding is due to patient selection, because both treatment groups undergoing angiography were highly comparable. After streptokinase infusion the patients received only subcutaneous heparin in a relatively low dose. This is a

TABLE I Baseline Characteristics of Both Treatment Groups

	Aspirin (n = 24)	Placebo (n = 26)
Age (yrs)	57 ± 10	59 ± 9
M/F	18/6	21/5
Previous AMI (n)	2	3
Previous angina pectoris (n)	3	3
Platelet count at admission (10^9/liter)	237 ± 65	251 ± 65
Interval first symptoms to thrombolysis (min)	137 ± 65	107 ± 62
Echo wall motion score day 1	8.7 ± 4.4	9.8 ± 5.3
Echo wall motion score day 3	8.3 ± 4.6	9.4 ± 5.1

Data are mean ± standard deviation.
AMI = acute myocardial infarction.

TABLE II Three-Month Follow-Up in Both Treatment Groups

	Aspirin (n = 24)		Placebo (n = 26)
Unstable angina pectoris (n)	8		6
Recurrent myocardial infarction (n)	1	*	6
Coronary angioplasty (n)	1		1
Death (n)	2		2

* p = 0.11, chi-square test, 2-sided.

TABLE III Characteristics of Patients With and Without Angiography in Both Aspirin and Placebo Treatment Groups

	Angiography (n = 25)	No Angiography (n = 25)
Age (yrs)	54 ± 10	62 ± 8
M/F	20/5	19/6
Unstable angina pectoris (n)	8 (3/5)	6 (5/1)
Recurrent myocardial infarction (n)	4 (0/4)	3 (1/2)
Coronary angioplasty (n)	2 (1/1)	0
Death (n)	0	4 (2/2)
Echo wall motion score day 1	8.8 ± 4.8	9.9 ± 5.2
Echo wall motion score day 3	8.6 ± 4.4	9.2 ± 5.4

Data are mean ± standard deviation.

TABLE IV Angiographic Results in Both Aspirin and Placebo Treatment Groups

	Aspirin (n = 9)	Placebo (n = 16)	p Value
Interval thrombolysis to angiography (days)	27 ± 12	29 ± 17	NS
Occlusion of LAD coronary artery (n)	1	12	<0.01*
Residual stenosis of LAD coronary artery (%)	83 ± 18	78 ± 23	NS
Significant (>70%) stenosis in right or circumflex system (n)	1	3	NS
LV ejection fraction (%)	60 ± 17	50 ± 15	0.13†
LV end-diastolic volume index (ml/m^2)	95 ± 29	121 ± 42	0.19†

LAD = left anterior descending; LV = left ventricular; NS = difference not significant.
* chi-square test, 2 sided.
† student *t* test, 2 sided.

generally accepted prophylactic regimen against deep venous thrombosis, but might be insufficient for the prevention of coronary reocclusion. In other trials of intravenous thrombolysis, patients have been treated with oral anticoagulants and found to have higher patency rates of the infarct-related coronary artery[11] than our patients in the placebo group. However, our angiographic results with aspirin are even better, which correlates well with the general results of our study. Further, aspirin treatment is safer, more convenient and less laborious than oral anticoagulation.

We have shown a low 3-month mortality rate in patients with anterior wall AMI, which might be due to the early thrombolytic treatment. This stresses the need for preservation of the excellent results of early thrombolysis in anterior wall AMI also reported by others.[1,2] Unlike coronary angioplasty,[4,5] platelet inhibition by low dose aspirin might offer this preservation, although angiographic studies with larger numbers of patients are necessary to confirm these results.

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Treatment of Recurrent Restenosis with Repeat Percutaneous Transluminal Coronary Angioplasty

PATRICK JOLY, MD
RAOUL BONAN, MD
DONALD PALISAITIS, MD
ANGEL CEQUIER, MD
JACQUES CRÉPEAU, MD
GILLES COTÉ, MD
PIERRE DE GUISE, MD
DAVID D. WATERS, MD

Among 2,000 patients who underwent PTCA at the Montreal Heart Institute between July 1980 and December 1986, 343 developed restenosis and had a second PTCA; 36 of these patients developed restenosis a second time and underwent a third PTCA. Indications for the third PTCA were reappearance of angina with a positive symptom-limited treadmill exercise test or unstable angina in association with angiographic documentation of restenosis. An additional 50 patients developed recurrent restenosis and were treated medically or with coronary bypass surgery, rather than a third PTCA. Choice of treatment appeared to be influenced more by the opinion of the treating cardiologist and the wishes of the patient than by clinical or angiographic factors; therefore, the patients who had a third PTCA are generally representative.

All PTCA procedures were performed by a percutaneous femoral approach, as previously described.[6] Based on our early experience,[7] since April 1983 we have used higher inflation pressures (8 to 12 atmospheres) and balloons that when inflated are slightly larger in diameter than the adjacent normal coronary segment. As a consequence, balloon/artery ratio in the study patients was higher ($p < 0.01$) for the third PTCA (1.14 ± 0.01) compared with either the second (1.07 ± 0.2) or the first (1.04 ± 0.1). Residual stenosis was less after the second PTCA (29 ± 12%, $p < 0.01$) compared with the first (33 ± 11%) and less after the third PTCA (27 ± 17%, $p < 0.01$) compared with the second.

Primary success was defined as a reduction in diameter stenosis to <50% in the absence of myocardial infarction, death or bypass surgery. All patients took aspirin during follow-up. Coronary arteriography was

From the Department of Medicine, Montreal Heart Institute, and the University of Montreal Medical School, Montreal, Quebec, Canada H1T 1C8. Manuscript received September 21, 1987; revised manuscript received and accepted December 14, 1987.

The most important limitation of percutaneous transluminal coronary angioplasty (PTCA) continues to be restenosis, which occurs at a rate of 30 to 40%.[1–3] Most patients with restenosis undergo a second PTCA; the primary success rate is high, the complication rate is low and sustained improvement of the redilated lesion has been demonstrated.[4,5] Patients who have recurrent restenosis comprise a much smaller group and reported information describing their management and outcome is scant. This article reports our experience on the safety and efficacy of a third PTCA for recurrent restenosis.

repeated a mean of 12.2 ± 9 months after the third PTCA in 30 of the 33 patients with successful PTCA. Restenosis was defined as a diameter stenosis >50% at a site with primary success. All measurements were made by an experienced cardiovascular radiologist, as previously described.[8] Statistical comparisons were made using analysis of variance, t tests or chi square tests, where appropriate.

A third PTCA was performed in 32 men and 4 women. Their clinical features are listed in Table I and compared with a control group with a successful first PTCA without restenosis. Control subjects were matched to study patients for age, gender and date of PTCA. The duration of angina was shorter, previous myocardial infarction was less common and hypercholesterolemia was more common in the group with recurrent restenosis.

The clinical evolution of the study patients is summarized in Figure 1. The interval between the first and second PTCA was 3.8 ± 2.3 months and between the second and third it was 4.0 ± 2.0 months. The site of dilatation was the left anterior descending coronary artery in 26 patients, the right coronary artery in 8 and the circumflex in 2. The mean stenosis reduction was from 85 ± 10 to 33 ± 11% with the first PTCA, from 79 ± 12 to 29 ± 12% with the second and from 76 ± 13 to 27 ± 17% with the third PTCA. Primary success was obtained in 33 of 36 patients (92%). The lesion could not be crossed in 1 patient whose angina was subsequently controlled with medical therapy. Two patients suffered complications: 1 developed left anterior descending coronary artery dissection necessitating emergency bypass surgery and another had a non-Q-wave infarction after PTCA of a right coronary artery.

Coronary arteriography was done a mean of 12.2 ± 9 months after PTCA in 30 of the 33 patients (91%) with primary success. The 3 patients who refused angiographic restudy had no angina and no evidence of myocardial ischemia on their thallium exercise tests. Restenosis was found in 11 of the 30 restudied patients (37%). Four of these 11 were asymptomatic and had negative thallium exercise test results. In the other 7, angina had recurred a mean of 4.2 ± 2 months after PTCA. One of these patients underwent bypass surgery and the remaining 6 successfully underwent a fourth PTCA. Angina has not recurred in 4 of the 6; however, in 3 of these 4, follow-up is less than 6 months. One patient died suddenly 2 months after the fourth PTCA and the other developed angina with restenosis at 3 months. He had a fifth angioplasty, again had restenosis and finally underwent bypass surgery. Overall, 26 of 36 patients (72%) are asymptomatic at long-term follow-up after a successful third PTCA, excluding the effect of subsequent treatment. Including the results of bypass surgery and fourth PTCA, 32 of 36 patients (89%) are asymptomatic.

In our experience a third PTCA for recurrent restenosis is both safe and effective. The primary success rate (92%), complication rate (6%) and restenosis rate (37%) did not differ from the rates usually reported for first angioplasties.[1-3] At latest follow-up, most of our patients were free from angina.

TABLE I Characteristics of Patients with a Third Angioplasty Compared with a Control Group with Successful Angioplasty Without Restenosis

	Study Group (n = 36)	Control Group* (n = 36)
Mean age (yrs)	52 ± 9	52 ± 7
Systemic hypertension (%)	12 (33)	15 (42)
Diabetes mellitus (%)	6 (17)	3 (8)
Family history (%)	24 (67)	20 (56)
Cigarette smoking (%)	16 (44)	14 (39)
Serum total cholesterol >240 mg/dl (%)	16 (44)	6 (17)†
Previous myocardial infarction (%)	3 (8)	11 (31)†
Duration of angina before first PTCA (mos)	9 ± 22	21 ± 35†
Number of arteries with diameter stenoses ≥70%: 1 (%)	24 (66)	22 (61)
2 (%)	10 (28)	11 (31)
3 (%)	2 (6)	3 (8)

* Matched to study patients for age, gender and date of angioplasty.
† $p < 0.05$.

Previous studies have reported on the efficacy of a second PTCA for restenosis. Williams,[4] Meier[5] and their co-workers concluded that the incidences of restenosis are similar after a first or second PTCA. Their angiographic follow-up rates, however, were only 48 and 61%. Our experience supports the contention that repeat PTCA can be performed with the usual restenosis rate; the high angiographic follow-up rate (91%) increases the precision of our results.

Abi-Mansour et al[9] reported good clinical results after a third PTCA in 17 patients; the restenosis rate was only 24%, but most patients did not undergo repeat arteriography. Teirstein et al[10] reported a primary success rate of a third PTCA of 93% (69/74), similar to our study. Complications included urgent surgery in 3 patients and 2 deaths. The per patient restenosis rate was 42%, and after a fourth PTCA, 53% (8/15). They concluded that restenosis rates are higher following third and fourth angioplasties. Our results do not support their conclusion. Additional information not in-

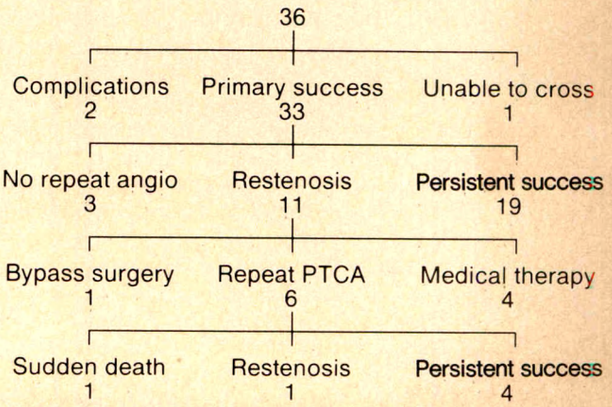

FIGURE 1. Clinical evolution of the 36 patients who underwent a third PTCA for recurrent restenosis.

cluded in their report might resolve this discrepancy. Restenosis rates vary according to the definition used, and per patient rates are higher after multivessel compared with single-vessel PTCA.

Restenosis has been correlated with procedural variables, such as the severity of residual stenosis and the absence of intimal dissection, and clinical variables, such as recent onset or unstable angina, diabetes and smoking.[11] Hypercholesterolemia, absence of previous infarction and shorter duration of angina were the clinical characteristics that differed in our study patients compared with a control group with no restenosis. Clinical factors such as these may reflect an underlying pathophysiologic tendency favoring restenosis. Procedural variables may be easier to manipulate; larger balloons and higher inflation pressures were used for the third PTCA in this study. The slightly milder residual stenoses that resulted may have favorably influenced subsequent restenosis rates.

In summary, a third PTCA is safe and effective treatment for recurrent restenosis. Although some patients may later require bypass surgery or another PTCA, most will eventually be asymptomatic.

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Effect of Nifedipine on Out-of-Hospital Silent Myocardial Ischemia in Asymptomatic Men with Coronary Artery Disease

PETER F. COHN, MD
WILLIAM E. LAWSON, MD
With the technical assistance of
VIRGINIA GENNARO
DOROTHY BRADY

Most investigations using ambulatory electrocardiography to document episodes of myocardial ischemia during daily life have studied patients with angina.[1-7] This is also true of therapeutic trials with antiischemic agents.[5-7] Recently, however, 3 studies[8-10] have reported the frequency and duration of ischemic episodes in coronary artery disease patients who do not have angina, i.e., patients asymptomatic after myocardial infarctions or those who have never had symptoms. Information on drug therapy for these patients with silent myocardial ischemia is confined to 1 study with the β blocker metoprolol.[11] The purpose of the present pilot study was to test the effect on silent myocardial ischemia of the calcium antagonist nifedipine as used in standard therapeutic doses.

From the Cardiology Division, Department of Medicine, State University of New York Health Sciences Center (T-17-020) Stony Brook, New York. This study was supported in part by a grant from Pfizer Laboratories, Inc. Manuscript received October 28, 1987; revised manuscript received and accepted December 10, 1987.

Our original patient group consisted of 15 male patients studied in our unit because of (1) no history of angina or anginal equivalents, (2) a positive but asymptomatic exercise test result and (3) coronary artery disease documented by coronary arteriography. None of the patients was taking cardiac medications during the exercise tests or the subsequent ambulatory monitoring period. Twelve of the 15 patients demonstrated >1 episode of ischemia on ambulatory electrocardiographic (Holter) monitoring during the initial 48 hours of monitoring and formed the final study group.

Ambulatory electrocardiographic monitoring was performed (usually using leads V_1 and V_5) with a Del Mar Avionics 445B 2-channel recorder, which has a frequency response of 0.50 to 100 Hz and meets the American Heart Association's specifications for heart rate and ST changes. In our laboratory this system has been tested for reliability by comparing conventional 12-lead electrocardiographic recordings during exercise tests to simultaneous Holter recordings. Before a study, each patient underwent positional changes and hyperventilation to assess lability of the ST segment; no baseline ST abnormalities were present, nor did any develop during these maneuvers. Recordings were scanned on an Avionics 9100 scanner; electrocardiographic strips showing horizontal or downsloping ST-segment depression of at least 1 mm, lasting at least 1 minute and separated by 1 or more minutes from successive episodes were printed out and reviewed in a blinded fashion. Patient diaries were also kept with patients instructed to record their daily activities on an hourly basis, except, of course, when

TABLE I Clinical, Angiographic and Holter Findings

					Holter Monitoring			
					Pretreatment		Nifedipine Treatment	
	Narrowed CA							
Pt	Right	LAD	LC	MI	Ischemic Episodes (n)	Duration of Ischemic Episodes (min)	Ischemic Episodes (n)	Duration of Ischemic Episodes (min)
1	+	+	+	0	11	699	4	143
2	+	0	0	0	6	153	4	144
3	+	+	0	+(A)	4	15	1	2
4	0	+	+	+(A)	6	53	1	10
5	+	+	+	0	3	39	4	21
6	+	+	+	+(I)	17	120	5	59
7	+	0	0	0	4	14	1	2
8	+	+	0	0	8	40	0	0
9	+	+	+	0	6	37	6	55
10	0	+	0	0	4	197	7	177
11	+	+	+	+(A)	5	52	0	0
12	+	+	+	0	6	68	4	2

A = anterior; CA = coronary artery; I = inferior; LAD = left anterior descending coronary artery; LC = left circumflex coronary artery; MI = myocardial infarction.

asleep. After giving informed consent, each patient was monitored for 48 hours consecutively and then given nifedipine therapy, either 10 or 20 mg orally 3 times a day. (Two patients received the larger dose because they had previously required it for blood pressure control). Two to 3 days later, patients underwent repeat 48-hour Holter monitoring.

Coronary arteriography was performed in a standard manner. A significant lesion was one that occluded a major coronary artery or one of its large branches by at least 70%.

All 12 patients were men aged 42 to 67 years. Three patients had prior Q-wave myocardial infarction (1 was unrecognized), and 1 patient had a prior non-Q-wave infarction. The site of the infarctions and vessel stenoses on coronary arteriography is listed in Table I. Six of the 12 patients had 3-vessel disease.

During the initial 796 hours of monitoring there were 80 episodes of silent ischemia. The number ranged from 3 to 17 (Table I). Total duration was 1,487 minutes with a range of 14 to 699 minutes. Heart rate at onset of ST depression ranged from 60 to 150 beats/min with a mean of 88 ± 8. As recorded in the diaries, activity during these episodes was usually not related to heavy exertion. A circadian variation was found: 32 of the 80 episodes (40%) occurred in the 6 A.M. to 12 noon time period.

The total number of ischemic episodes decreased to 37 ($p < 0.01$) and the duration of 625 minutes ($p < 0.05$) (Table II). As depicted in Table I, 7 of the 12 patients showed at least a 50% decrease in both the number and duration of episodes. Of the other 5, 2 (patients 2 and 12) had lesser reductions, and 3 (5, 9, 10) had no reduction in frequency but a reduction in duration. In 2 patients, ischemia was eliminated entirely and in 3 others, reduced to 1 episode. Heart rate at the onset of ischemic events was unchanged from that before therapy (Table II) and there was no change in frequency of episodes between 6 A.M. and 12 noon. There were no adverse side effects from the drug.

TABLE II Effect of Treatment on Holter Findings

	Pretreatment	During Nifedipine Administration	p Value
Ischemic episodes (n)	80	37	<0.01
Duration of ischemic episodes (min)	1,487	625	<0.05
Heart rate at onset of episodes (beats/min)	87	88	NS
Episodes occurring between 6 A.M. and 12 noon (%)	40	42	NS

NS = difference not significant.

To date, 3 studies of asymptomatic patients with coronary artery disease and silent myocardial ischemia out-of-hospital have been published.[8-10] Whether these patients should be treated and if so, with what agents, is unclear because pertinent prognostic data are limited. What studies are available show that prognosis in asymptomatic coronary populations with silent ischemia on exercise testing (with or without prior infarctions) appears to be related to the extent of vessel disease and the degree of left ventricular dysfunction. Certainly, if one were going to treat an asymptomatic population with antiischemic drugs, the subgroup of high-risk patients with 3-vessel disease and moderate left ventricular dysfunction would seem best suited for such trials (although coronary artery surgery is also an option in these patients). But what agents—or combinations of agents—should one choose? Choice of drugs can be empiric (based on antianginal experience) or can depend on the results of pilot studies with asymptomatic patients. In our pilot study, we used nifedipine, a calcium antagonist with well-documented coronary vasodilatory properties, because increased vasoconstrictor tone as a contributing mechanism to silent ischemia has been suggested by (1) the lower

than expected heart rates observed during many silent ischemic episodes and (2) the relative infrequency of episodes related to strenuous exertion. In the present study we used standard doses of the drugs and no attempt was made to titrate to higher levels.

One of the warnings in interpreting our study data is day-to-day variability of ischemic episodes. This is especially important since this was not a randomized placebo-controlled trial. Preliminary studies by Deanfield et al[12] suggest that for a trial of this size, one would need to show at least a 50% decrease in ischemic episodes before one could attribute the reduction to therapeutic agents. In our study, this level was achieved. Further, despite the use of just 1 drug at low doses, 9 of the 12 patients had marked improvement in both ischemic frequency and duration.

Our reduction in ischemic frequency and duration is comparable to that achieved by Imperi et al[11] using low dose metoprolol (50 mg 2 times daily) although the mechanisms of action of these 2 drugs are obviously different. Even after treatment, we found the percentage of ischemic activity was still highest from 6 A.M. to 12 noon. This was also true in the study by Imperi et al.

In summary, even in standard dosages, nifedipine was effective in reducing the frequency and duration of silent myocardial ischemia in our patient population. Based on this initial pilot study, it would appear reasonable to consider nifedipine for testing in large scale, randomized, placebo-controlled studies of asymptomatic patients with silent ischemia. (If higher doses are used, however, they probably should be combined with β blockers to reduce reflex tachycardia). These trials could be designed to explore not only the therapeutic benefits of antiischemic drugs, but also the prognostic implications of treating ischemic episodes—whether they are painful or not.

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Relation of Left Ventricular Free Wall Rupture in Acute Myocardial Infarction to Forced Immobilization

CHRISTIAN TORP-PEDERSEN, MD
FRANK STEENSGAARD HANSEN, MD
ASGER PEDERSEN, MD

Left ventricular (LV) free wall rupture occurs in approximately 10% of fatal acute myocardial infarctions (AMI).[1] In 1 report[2] 73% of the deaths associated with myocardial infarcts among institutionalized psychotic patients were due to LV rupture. This raised the possibility of a relation between physical activity and LV rupture. In a later report[3] no difference was observed between psychotic and nonpsychotic patients at the same hospital. At present it is unclear whether physical activity is a risk factor for LV rupture in myocardial infarcts. We studied 7,009 consecutive cases of AMI for a possible relation between mobilization and LV rupture.

From the Department of Cardiology, Glostrup County Hospital, DK2600 Glostrup, Denmark.

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Glostrup County Hospital serves a well-defined urban and suburban area in Copenhagen, Denmark, with a population between 250,000 and 350,000. The coronary care unit receives all cardiac emergencies in the region. AMI is rarely treated at home. We have analyzed all cases of AMI admitted during the period 1959 to 1983. From 1959 to 1977 the diagnosis of AMI was based strictly on the World Health Organization criteria.[4] After 1977 a transient increase in serum levels of the heart-specific creatine kinase isoenzyme in patients with a supposed onset of AMI within the preceding 36 hours was considered a prerequisite for the diagnosis. In a study from this department[5] positive and negative predictive values of the transient increases in creatine kinase isoenzyme were 0.98 and 1.00 compared with the World Health Organization criteria.

AMI was assumed to take place at the onset of severe chest pain. This time was well defined in all cases of LV rupture but 6. In all patients with LV rupture who survived more than a few hours after admittance, increased levels of creatine kinase isoenzyme or aspartate aminotransferase were demonstrated. In no case did autopsy indicate that the infarct was older than estimated by the onset of chest pain.

Postmortem examination was performed routinely in all patients who died from known or suspected AMI. Data were available in 91% of fatal cases. The

TABLE I Influence of Age and Sex on Relative Risk of Left Ventricular Rupture in Acute Myocardial Infarction (n = 7,009)

Age (yrs)	Men	Women	Both
<40	0	0	0
40–49	0.2 (0.1–0.5)	0.4 (0.2–2.6)	0.2 (0.1–0.5)
50–59	0.4 (0.2–0.6)	0.8 (0.4–1.7)	0.4 (0.3–0.6)
60–69	0.9 (0.7–1.3)	1.5 (0.9–2.3)	1.1 (0.8–1.5)
70–79	1.6 (1.1–2.3)	1.7 (1.1–2.5)	1.8 (1.3–2.4)
≥80	2.6 (1.6–4.3)	2.9 (1.8–4.6)	2.9 (2.1–4.2)
Total	0.6 (0.4–0.8)	1.8 (1.3–2.4)	

Data in parentheses are 95% confidence limits. The risk of left ventricular rupture increases steeply with age ($p < 0.0001$) and is higher for women ($p = 0.002$).

TABLE II Influence of Immobilization on Left Ventricular Rupture in Acute Myocardial Infarction

	1959 to 1969 Immobilization	1969 to 1983 Immobilization
	+	0
Infarctions (n)	907	6,102
Deaths (n)	269 (30%)	1,263 (21%)
Ruptures (n)	24 (2.7%)	165 (2.7%)
Place of LV rupture		
Bed	19 (79%)	132 (80%)
Out of bed	0	12 (7%)
Lavatory	0	10 (6%)
Unclear	5 (21%)	11 (7%)
Total	24 (100%)	165 (100%)

Before 1968 patients with acute myocardial infarction were immobilized for the first days after onset; after 1968 patients were allowed to move about freely.

LV = left ventricular; + = present; 0 = absent.

diagnosis of LV rupture was based on the findings of an infarction and a hemipericardium. In most cases a perforation was located within the infarct. In a minority of cases where the perforation was not obvious, a dissecting infiltration of blood into the myocardium was demonstrated. Infarct-related septal defects were not included in this investigation.

From 1959 to 1966 patients with suspected AMI were strictly immobilized during the first days and then gradually mobilized. From 1966 to 1968 patients were allowed to get out of bed from the first day on. After 1968 no immobilization was imposed, and all patients with AMI were allowed to move about freely in the department (monitored by telemetric equipment) from the first day on.

Statistical analysis of contingency tables was performed with the chi-square test, for 2 × 2 tables with Yates correction. Relative risks (fraction of LV ruptures in risk group divided by fraction of LV ruptures in group without risk) and their 95% confidence intervals were calculated as described by Katz et al[4] assuming near normal distribution for ln (relative risk). No corrections were made for the frequency of autopsy.

During the period 1959 to 1983, 7,009 patients were admitted to Glostrup County Hospital with a confirmed AMI. Of these 1,532 died during admission (mortality rate 23%). An LV rupture of the free wall of the heart was demonstrated at autopsy in 189 cases: 2.7% of all patients with AMI and 12% of fatal cases.

Table I lists the calculated relative risk of LV rupture in each age and sex group with AMI. The relative risk increases steeply with age ($p < 0.0001$), almost doubling with each decade.

Figure 1 shows the interval from onset of anginal pain to occurrence of LV rupture. One-third of all LV ruptures occurred within 24 hours of onset of AMI. The latest occurred 61 days after onset of AMI. Positive evidence of reinfarction preceding LV rupture was not demonstrated in any case, either clinically or by autopsy.

Data on the site of AMI were available in 3,253 cases. Of these 43% were anterior infarctions by standard electrocardiographic criteria, 39% were inferior infarctions and 17% were indefinite or had other location. Among the 189 LV ruptures 61% were anterior infarctions (autopsy), 32% inferior infarctions and 7% indefinite or had other location. Assuming that distribution of infarct site for the 3,223 cases is representative for the whole series, the relative risk of LV rupture is 2.1 (95% confidence interval 1.5 to 2.7) in anterior infarction and 0.7 (0.5 to 1.0) in inferior AMI ($p < 0.0001$).

LV rupture occurred during the first AMI in 164 cases (87%), during the second AMI in 21 cases (11%) and during the third AMI in 1 case. In 3 cases the number of previous AMIs could not be stated.

Twenty-eight patients had a history of systemic hypertension (15%), while 156 patients (83%) did not have hypertension. The average blood pressure at admission was 146/93 mm Hg; 44 patients had a systolic blood pressure >160 mm Hg and 16 a diastolic blood pressure >110 mm Hg. On the day of LV rupture average blood pressure was 126/85 mm Hg; 11 patients had a systolic blood pressure >160 mm Hg and 7 a diastolic blood pressure >110 mm Hg.

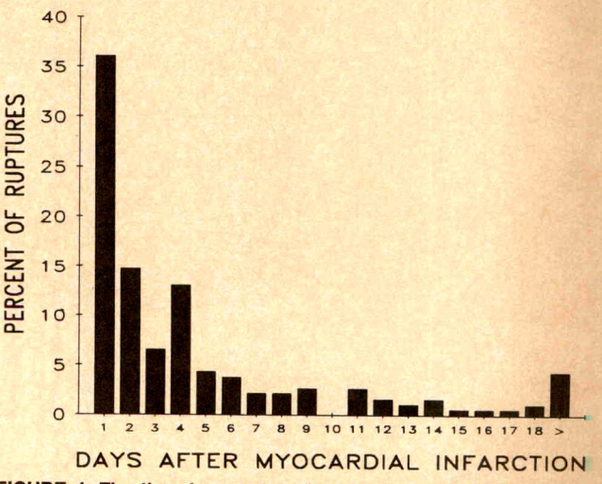

FIGURE 1. The time from onset of acute myocardial infarction to occurrence of left ventricular rupture is shown for 183 of 189 consecutive cases of left ventricular rupture of the free wall of the heart in patients with acute myocardial infarction. In the remaining 6 cases time of onset could not be determined. > = left ventricular ruptures occurring 19 days after acute myocardial infarction or later.

Table II lists the incidence of LV rupture in patients with AMI with and without forced immobilization.

Data were also analyzed for relation between site of AMI, age, activity at time of LV rupture and time of AMI. For pairwise analysis all p values were >0.14.

This is the only large series of patients with unselected AMI defined by modern criteria where a high frequency of autopsy allowed estimation of incidence and risk factors of LV rupture. The increased risk with high age and female sex that we found is as expected. Our finding that LV rupture is an early event—and the lack of relation with systemic hypertension—agrees with some investigations and disagrees with others.[1]

In our institution patients have been allowed to move about freely since 1968 and the frequency of LV rupture has not changed. Even among the nonimmobilized patients most LV ruptures occurred while the patient was in bed. Only 12 LV ruptures among 6,102 patients with AMI actually took place while the patient was sitting or walking. We conclude that there is no advantage to forced immobilization with respect to risk of LV rupture.

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Assessment of Left Ventricular Volume Changes During Exercise Radionuclide Angiography in Coronary Artery Disease

PIERCE J. VATTEROTT, MD
RAYMOND J. GIBBONS, MD
DAVID C.K. HU, MD
MANUEL L. BROWN, MD
IAN P. CLEMENTS, MD

During exercise radionuclide angiography, the effect of exercise on left ventricular (LV) volumes has been inferred from changes in LV counts.[1,2] A single published study using in vivo labeling techniques found that the radiotracer concentration per milliliter of blood did not remain constant during exercise.[3] This finding implies that measurement of LV volume during exercise based on a single determination of blood radioactivity is not valid. We have evaluated the effect of exercise on hematocrit and blood radioactivity concentration after technetium-99m in vivo-in vitro labeling.

We studied 13 subjects (12 men, 1 woman; mean age 59 years) referred for exercise radionuclide angiography for assessment of coronary artery disease. Erythrocytes were labeled by the in vivo-in vitro labeling technique described by Callahan et al.[4] For this study, an additional central intravenous line catheter was inserted through the basilic vein. The catheter was positioned with its tip resting in a central vein within the thorax. A separate peripheral intravenous line was inserted. A 10-ml resting sample of venous blood was obtained through each line while the subject was at rest. The patients then underwent symptom-limited supine bicycle exercise; a set of 10-ml venous samples were obtained at peak exercise and at 6 minutes after exercise. Immediately after exercise, the tubes of blood were placed on the center of the collimator of the gamma camera, and blood radioactivity was measured for 2 minutes. The hematocrit of each sample was measured by centrifuge.

Changes in blood radioactivity and hematocrit were evaluated for statistical significance by the paired t test.

Age, sex, medications, exercise duration, maximal workload, reasons for stopping exercise and baseline and peak blood pressures and heart rates for each patient are shown in Table I. Blood radioactivity did not increase during exercise (Figure 1), but hematocrit value did (Figure 2). The mean central hematocrit value increased from a resting value of 40% to 42% at peak exercise (p = 0.001) and to 42% after exercise (p = 0.001). Twelve of the 13 patients had increases in hematocrit. The mean peripheral hematocrit value increased from 41% at rest to 42% at peak exercise (p = 0.308) and to 43% after exercise (p = 0.013). Eleven patients had increases.

Using the in vivo technique for erythrocyte labeling, Konstam et al[3] found that blood radioactivity increased with exercise. LV volume calculations based on a single resting blood activity measurement could therefore result in overestimation of exercise volumes by as much as 20%.[3] With the in vivo technique, multiple blood samples would be necessary to determine volume changes with exercise.

A major difference between this study and that of Konstam et al[3] is the labeling technique. Callahan et al[4] evaluated the in vivo labeling technique with stannous DTPA and found that labeling efficiency increased slowly from 62% at 30 seconds to an equilibrium value of 95% in 10 minutes. A significant amount of free pertechnetate is distributed throughout the

From the Division of Cardiovascular Diseases and Internal Medicine and the Department of Diagnostic Radiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905.
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TABLE I Summary of Relevant Data

Pt	Age (yr), Sex	Drugs	Exercise: Duration (min)	Exercise: Max. Work (kpm)	Exercise: Reason for Stopping	SBP (mm Hg): Baseline	SBP (mm Hg): Peak	HR (beats/min): Baseline	HR (beats/min): Peak	HR × SBP Product
1	56, M	0	9.8	1,200	Leg fatigue	130/85	200/85	60	132	26,400
2	53, M	C	9.0	900	Dyspnea, angina	130/95	210/90	70	122	25,620
3	63, F	0	6.0	300	Dyspnea	140/90	210/80	60	112	23,520
4	55, M	B	6.0	600	Leg fatigue	140/90	165/90	61	102	16,830
5	59, M	B	9.0	900	Leg fatigue	138/82	212/86	58	125	26,500
6	73, M	C, B	6.0	400	Fatigue	110/70	140/70	47	64	8,960
7	67, M	B, D	6.0	500	Leg fatigue	176/84	186/94	65	104	19,344
8	56, M	0	6.0	500	Leg fatigue, angina	130/80	190/85	84	133	25,270
9	62, M	0	3.1	300	Dyspnea	140/100	160/110	74	111	17,760
10	61, M	B	6.0	600	Leg fatigue	120/84	160/90	59	100	16,000
11	43, M	B	8.3	600	Orthopedic pain	120/80	160/100	62	108	17,280
12	62, M	0	6.4	600	Leg fatigue	130/80	175/100	60	92	16,100
13	52, M	0	10.3	750	Leg fatigue, angina	150/90	170/—	70	140	23,800

B = β blocker; C = calcium antagonist; D = diuretic; HR = heart rate; SBP = systolic blood pressure.

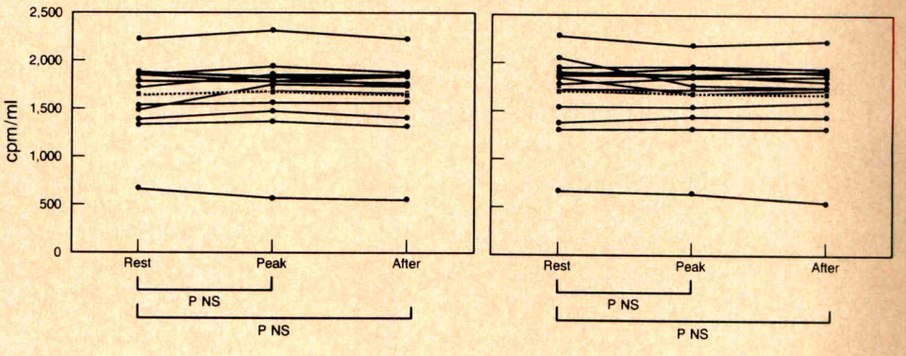

FIGURE 1. Blood radioactivity at rest, peak exercise and after exercise. *Broken line* = mean values. *Left*, central venous blood; *right*, peripheral venous blood.

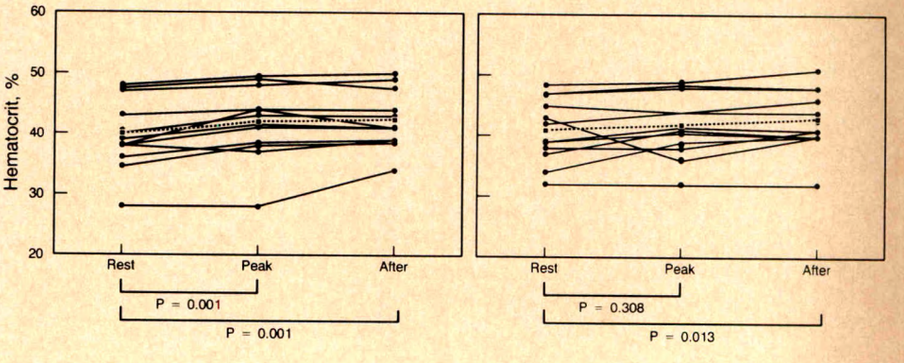

FIGURE 2. Blood hematocrit value at rest, peak exercise and after exercise. Broken line = mean values. *Left*, central venous blood; *right*, peripheral venous blood.

body. With the in vivo-in vitro labeling technique, approximately 90% of the technetium-99m pertechnetate is bound firmly to erythrocytes and less free pertechnetate is available.

There are 2 possible explanations for our findings: (1) introduction of an unlabeled population of erythrocytes into the intravascular space or (2) concomitant hemoconcentration and loss of the technetium-99m label from the erythrocytes. The in vivo technique used by Konstam et al[3] may allow free pertechnetate to label erythrocytes outside the intravascular pool. A sequestered but labeled erythrocyte population may have been released into the circulation during exercise in their study, as opposed to an unlabeled population in this study.

The source of this unlabeled population of erythrocytes is uncertain. In animal studies, Vatner et al[5] found that the mean hematocrit value in dogs in-

creased from 40% to 49% during running and that this effect was abolished by splenectomy. The state of the human spleen during exercise is poorly understood. However, Gates and Ames[6] recently demonstrated decreasing splenic radioactivity during the maximum exercise phase of gated stress testing in 24 patients. Thus, it is possible that the human spleen has a sequestered erythrocyte population that is released under the influence of catecholamines during exercise.

Hemoconcentration during long- and short-term ergometer exercise has been reported.[7-9] The former is secondary to dehydration, and the latter is due, at least in part, to a small loss of protein from the vascular system. A loss of radionuclide from cell membranes could exist concomitant with hemoconcentration. This would be reflected as an increase in hematocrit value but as a smaller increase, no change or overall decrease in radionuclide level in the blood sample.

This study showed an increase in hematocrit value but no change in blood radioactivity during exercise radionuclide angiography using in vivo-in vitro labeling. This finding validates volume estimations throughout exercise based on a single blood sample. This is a significant advantage over the more commonly used in vivo method.

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Propafenone for Prevention of Recurrent Atrial Fibrillation

CHARLES R. KERR, MD
GEORGE J. KLEIN, MD
JAMES E. AXELSON, PhD
JOCELYN C. COOPER, RN

Propafenone, an investigational class 1C antiarrhythmic drug, is effective in the treatment of ventricular arrhythmias[1-5] and paroxysmal supraventricular tachycardia.[6] Relatively few studies have evaluated its effect on atrial flutter or fibrillation.[7] In this study we evaluated the efficacy of propafenone in the prevention of recurrent atrial fibrillation (AF).

Fifty-three patients (21 women, 32 men, mean age 53 ± 15 years) presenting with recurrent episodes of AF were studied. All patients had multiple episodes of AF, recorded at least once by electrocardiogram. All antiarrhythmic drugs except digoxin were discontinued a minimum of 5 half-lives before initiation of the study. Digoxin was continued in 14 patients with a rapid ventricular response to AF. Propafenone was started at an initial dose of 150 mg 3 to 4 times daily. Dosage adjustment was made at intervals of at least 72 hours. In patients with frequent episodes of AF, the dose was increased as necessary up to 300 mg 4 times daily and adjusted to the lowest level that prevented recurrence of AF. In patients with infrequent episodes, the dose was increased as tolerated up to 300 mg 3 times daily. Patients were advised to take the drug with food to enhance bioavailability.[8] Patients were asked to report any recurrence of arrhythmia. Patient compliance was monitored by visits every 6 to 12 weeks when pill counts were performed. The drug was withdrawn for either severe side effects not responding to dose reduction or inefficacy after reaching the maximum dose of 300 mg 3 to 4 times daily (total dose of 900 to 1,200 mg daily).

Of the 53 patients in the study, 48 had been previously treated with 1 or more antiarrhythmic drugs, whereas only 5 were treated with propafenone as their first drug. Of those patients previously treated, the mean number of drugs used was 3 ± 2 (standard deviation). Previous drug therapy could be divided into drugs that slowed the ventricular rate including digoxin (37 patients), β-blocking agents (30), verapamil (19), diltiazem (1) and those known to prevent AF, including quinidine (34), procainamide (15), disopyramide (15), sotalol (1) and amiodarone (1). Three patients had been receiving only drugs that principally slow ventricular rate, whereas 45 had been receiving only drugs to prevent AF, or a combination of the 2 groups. Drugs had been discontinued for side effects or inefficacy. In 1 patient amiodarone administration was stopped 3 months before the initiation of propafenone treatment. Recurrent AF had been present for

From the Division of Cardiology, Department of Medicine, and Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver V6T 2B5, and the Division of Cardiology, Department of Medicine, University of Western Ontario, Canada. This work was supported in part by grants from the British Columbia Heart Foundation, Vancouver, British Columbia, The Medical Research Council of Canada, Ottawa, Ontario, Canada, and Knoll Pharmaceutical Company of Canada. Dr. Kerr is a Scholar of the Medical Research Council of Canada. Manuscript received July 28, 1987; revised manuscript received and accepted November 23, 1987.

periods ranging from 2 months to 17 years (mean 5 ± 4 years). All patients had had more than 1 episode of AF, with 45 reporting over 5 episodes in the preceding 2 years and 36 over 5 episodes in the last year. Potentially contributory underlying heart disease was observed in 14 patients, mitral valve disease in 3, congestive heart failure in 6, previous myocardial infarction in 3, hypertrophic cardiomyopathy in 1 and previous atrial septal defect repair in 1. In the other 39 patients AF was considered primary.

Forty patients have had complete or partial success and continue receiving propafenone with a follow-up from 1 to 24 months (mean 9 ± 6). Thirteen have discontinued the drug after periods of 1 day to 7 months (mean 1 ± 2 months). Of the 40 patients with complete or partial success, 7 had significant heart disease whereas in 33 the AF was primary. The doses of propafenone in these 40 patients ranged from 300 to 1,200 mg daily (mean 700 ± 190 mg). The most common dosing regimens were 300 mg twice daily (14 patients) and 300 mg 3 times daily (13 patients).

Of those 40 who continued receiving propafenone, 34 have had complete or near-complete success, defined as complete absence of arrhythmia or rare episodes for which no additional therapy was indicated or requested by the patient. In these 34 patients, 26 had had over 5 episodes in the previous year. An additional 6 who previously had been receiving multiple drugs showed significant improvement. In all 6, propafenone was more effective than previous drugs and patients elected to continue receiving it. In 4 the episodes were less frequent with a slower ventricular rate whereas the other 2 remained in AF with a well-controlled ventricular rate. In 5 patients given propafenone as initial therapy, 4 had complete control and 1 stopped the drug due to side effects.

Of the 40 patients who continued receiving propafenone, 20 have had mild side effects (including 8 with headache or dizziness followed, in 7, by complete resolution). Eight complained of taste alteration, with subsequent resolution of this symptom in 4 and persistence of very mild and tolerable taste alteration in the other 4. Three patients complained of constipation, which was controlled by stool softeners. Three complained of fatigue, later resolved in 2. Thirty-three of these 40 patients either had no initial symptoms or had symptoms that have resolved. In 2 patients without preexistent evidence of conduction system disease, propafenone administration resulted in the suppression of sinus node function and the development of symptomatic bradycardias. Both had implantation of permanent pacemakers, continued receiving propafenone and evidenced complete arrhythmia control.

Propafenone was discontinued in 13 patients, 8 due to drug intolerance and 5 due to inefficacy. Three developed severe headache. Two developed dizziness and insisted on stopping the drug after 24 hours, without attempting dose manipulation. One had severe, persistent diarrhea. One asthmatic patient had an increase in bronchoconstriction. One had coincidental pacemaker failure (lead insulation failure with a resultant cardiac arrest) and elected to remain off the drug although the association of the drug to these events was unclear. Thus, the overall frequency of definite, persistent side effects was 14 in 53 patients (26%). Cessation of drug therapy due to possible side effects occurred in 15%, with the additional 11% having mild, persistent symptoms.

Of the 5 in whom the drug was tolerated but failed to control AF, 4 had underlying heart disease. One woman with a previous myocardial infarction had recurrent AF on a dose of 750 mg daily. She declined a dosage increase. A second patient with Wolff-Parkinson-White syndrome and AF was initially controlled with 1,200 mg daily of propafenone. However, he developed a severe alcoholic dilated cardiomyopathy and his AF now is diagnosed as chronic. A third patient with obstructive hypertrophic cardiomyopathy and atrial flutter had recurrent AF on 900 mg daily and is now receiving amiodarone to control it. A fourth patient with previous atrial septal defect repair and AF had electrical cardioversion performed while taking propafenone (900 mg daily). Sinus rhythm was restored for 48 hours before return to AF. Amiodarone also failed to maintain sinus rhythm and he remains in AF. A fifth patient, without heart disease, likely had chronic AF for 2 years. Electrical cardioversion during propafenone therapy (900 mg daily) restored sinus rhythm for 24 hours only and he now remains in AF. Corrected QT intervals before propafenone (QT_C = 0.42 ± 0.04 s) were not different than those during propafenone administration (QT_C = 0.41 ± 0.03 s, $p > 0.5$). No patient had more prolonged or more frequent episodes of AF.

Propafenone is an investigational antiarrhythmic drug extensively evaluated for treatment of ventricular arrhythmias. Its primary effect in ventricular and atrial myocardial cells and Purkinje fibers is the slowing of the rate of rise of phase 0 of the action potential (V_{max}).[9-11] The mechanism of AF is generally considered to be reentry within the atrial myocardium.[12-14] The mechanism of propafenone's action in preventing AF may be due to several factors. The depression in V_{max} may slow conduction and block 1 limb of the reentry circuit. The abolition of atrial premature beats may remove the trigger for the reentrant arrhythmia and the mild β-adrenergic antagonism may suppress sympathetic stimulation. In addition, propafenone, unlike type 1A antiarrhythmic drugs, may beneficially slow the ventricular response during AF.[15]

In the present study, we report the efficacy of propafenone in preventing recurrent AF in 53 patients. In 48 patients, other drugs had been either ineffective or led to intolerable side effects. Thus, the patient population was skewed to those with previous drug failures. In spite of this skewed population, propafenone was effective in controlling 34 of 53 patients with partial control in 6 more (overall 77%).

Ours was a nonrandomized, open-label study to assess drug efficacy. Thus, it is prone to errors and observer bias known to this type of study. Nonetheless, propafenone appeared to be effective in eliminating or reducing the frequency of episodic AF in a highly

symptomatic group of patients. Study design does not permit comparison to other drugs but it does suggest that propafenone is generally well tolerated and effective in controlling AF in many patients.

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Ventriculoatrial Conduction and Atrial Activation During Ventricular Flutter and Fibrillation

GUIDO CAPELLA, MD
PEDRO BRUGADA, MD
HEIN J.J. WELLENS, MD

Electrophysiologic studies have evaluated retrograde conduction over the atrioventricular (AV) conduction system during ventricular pacing.[1–3] From these studies it has become clear that ventriculoatrial conduction during ventricular pacing is present in about 70% of patients with normal AV conduction. It has also been shown that ventriculoatrial conduction is often present during ventricular tachycardia.[4] Little is known about presence and patterns of ventriculoatrial conduction during ventricular flutter (VFl) and fibrillation (VF).[5]

From the Department of Cardiology, Academic Hospital of Maastricht, University of Limburg, P.O. Box 1918, 6201 Bx Maastricht, The Netherlands. Manuscript received August 18, 1987; revised manuscript received December 2, 1987, and accepted December 4.

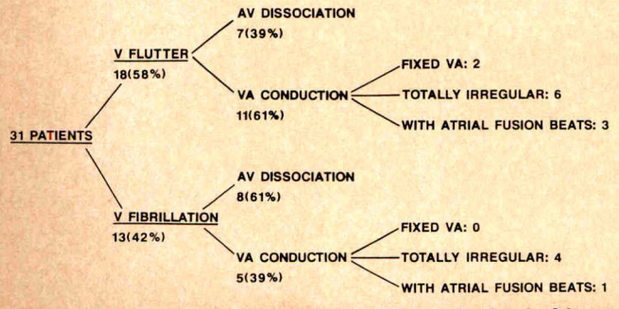

FIGURE 1. Patterns of ventriculoatrial (VA) conduction in 31 patients. A = atrium; V = ventricular.

We recently reviewed 31 patients in whom VFl or VF was induced during programmed stimulation of the heart and where at least 2 simultaneously recorded intracavitary atrial leads allowed the evaluation of mode and direction of atrial activation during VFl/VF. Patients in whom an accessory pathway was present and patients with abnormal AV conduction during atrial pacing were excluded. VFl was diagnosed when the ventricular rate was >260/min and a continuous sequence of sinusoidal waves was present on the surface electrocardiogram, making it impossible to distinguish the QRS complex from the ST segment and the T wave.

The analysis of the 31 patients revealed the following (Figure 1). In 15 patients (48%) there was no ventriculoatrial conduction during VFl/VF: atrial activation showed the same sequence as during sinus rhythm. In the remaining 16 patients (52%) ventriculoatrial conduction was present during VFl/VF. In these patients, 3 types of atrial activation were observed: (1) retrograde atrial activation with a completely irregular atrial response (Figure 2) was found in a total of 10 patients—6 patients during VFl and 4 patients during VF; (2) retrograde atrial activation with a fixed ventriculoatrial ratio and regular atrial response (ventriculoatrial ratio was 3:1 and 4:1) was observed in 2 patients, both with VFl (Figure 3); (3) anterograde atrial activation and retrograde atrial activation from ventriculoatrial conduction, with atrial fusion complexes, was found both during VFl (3 patients) and VF (1 patient). Periods of ventriculoatrial dissociation and retrograde atrial activation could be observed in the same patient (Figure 4). In these patients fusion P waves from anterograde and retrograde atrial activation were also observed.

During ventricular pacing at a rate of 100/min, 21 patients (64%) had 1:1 ventriculoatrial conduction. Five of them had complete ventriculoatrial dissocia-

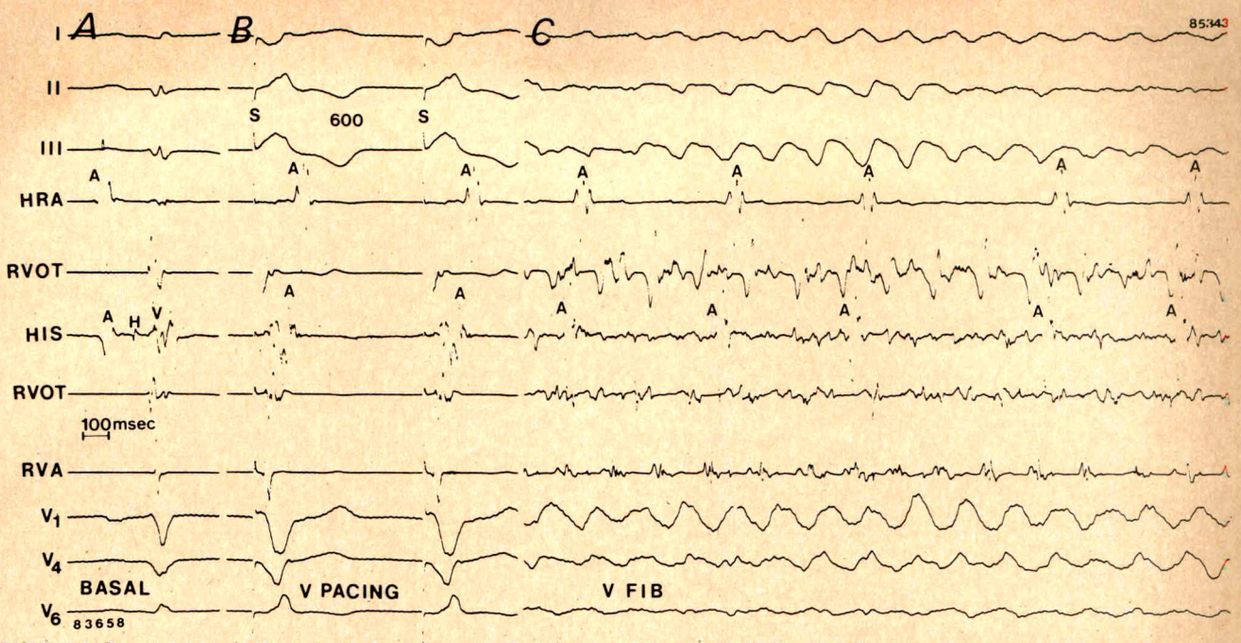

FIGURE 2. Completely irregular retrograde atrial activation during ventricular fibrillation (V FIB). *A*, anterograde atrial activation during sinus rhythm. *B*, retrograde atrial activation during ventricular pacing at 100/min. *C*, sequence of atrial activation during ventricular fibrillation. Note the complete irregularity of the AA intervals and the similarity to atrial activation in *B*. HRA = high right atrial recording; RVA = right ventricular apex; RVOT = right ventricular outflow tract.

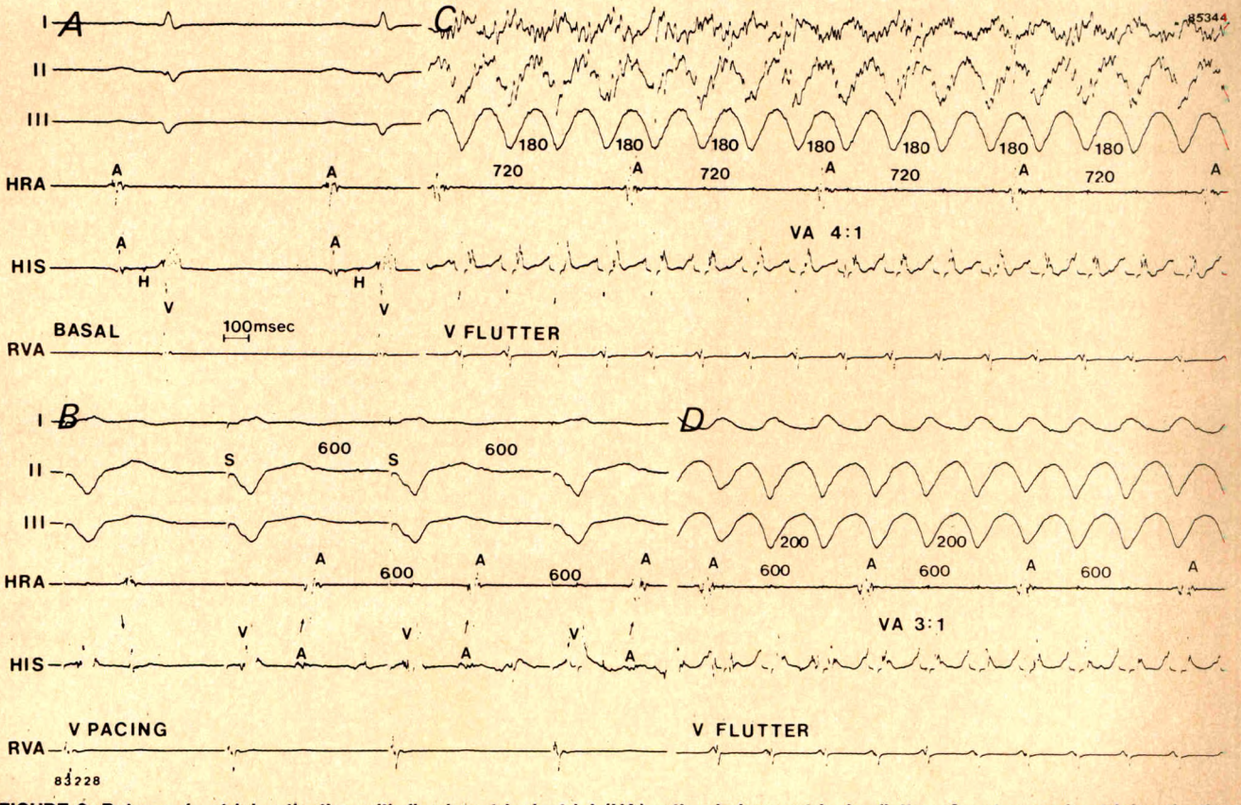

FIGURE 3. Retrograde atrial activation with fixed ventriculoatrial (VA) ratio, during ventricular flutter. *A*, anterograde atrial activation during sinus rhythm. *B*, retrograde atrial activation is present during ventricular pacing at 100/min after the second to fourth paced beat. *C*, 4:1 retrograde conduction during ventricular flutter at a rate of 330/min. *D*, 3:1 retrograde conduction during ventricular flutter at a rate of 300/min.

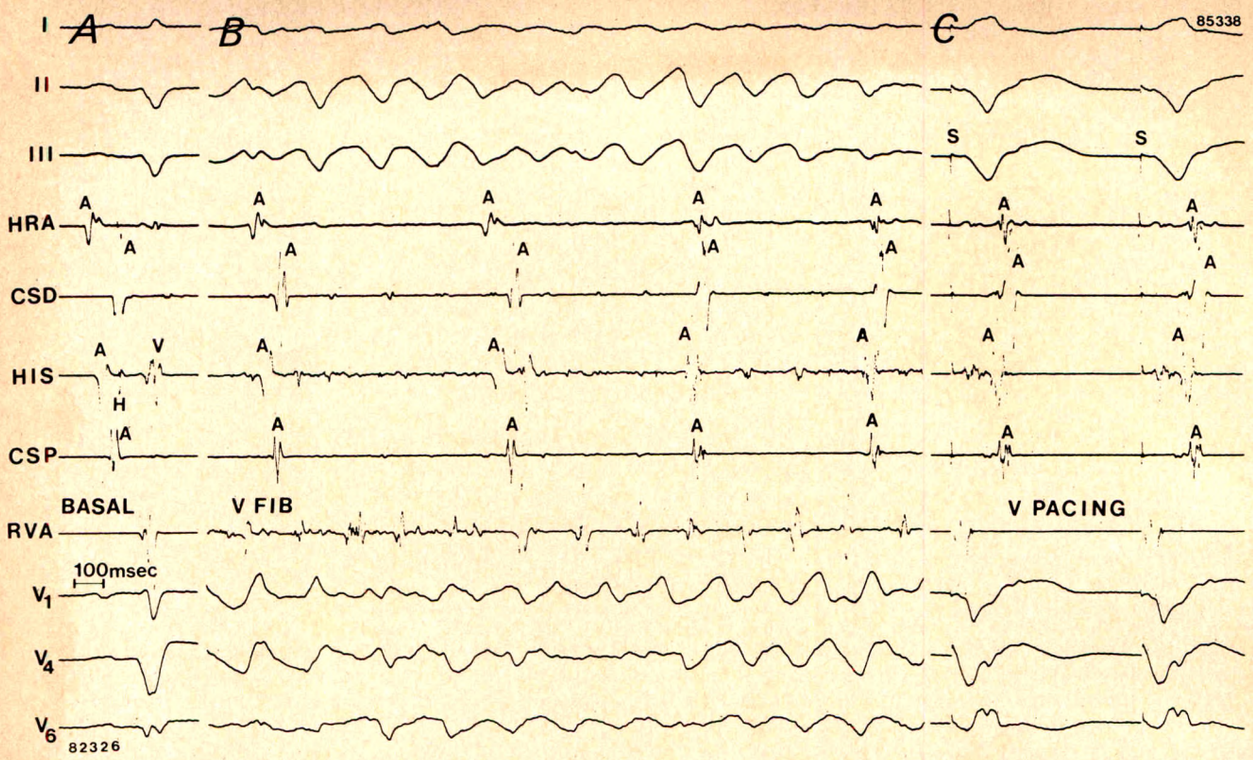

FIGURE 4. Anterograde and retrograde atrial activation in the same patient during ventricular fibrillation. On the *left* of *B*, the anterograde atrial activation is identical to the one during sinus rhythm, *A*. On the *right* of *B*, retrograde atrial activation occurs identical to that visible during ventricular pacing at 100/min, *C*.

tion during VFl/VF. No patient without ventriculoatrial conduction during ventricular pacing at a rate of 100/min subsequently showed ventriculoatrial conduction during VFl/VF. Looking at the ventriculoatrial ratio in patients with ventriculoatrial conduction during VFl/VF, we found a fixed ventriculoatrial ratio in only 2 patients, both with VFl. A 3:1 and 4:1 ratio occurred at ventricular rates of 300 and 330/min, respectively. When ventriculoatrial conduction occurred during VFl with higher rates and during all cases of VF, atrial activation showed a completely irregular pattern.

In 1976 Scher et al[6] reported on retrograde depolarization of AV junctional tissue during VF in the dog. Using histograms and autocorrelograms, they concluded that atrial depolarization intervals did not remain constant but varied widely. They postulated that during retrograde conduction the AV junctional tissues during VF behaved similarly to the anterograde direction during atrial fibrillation. Which cardiac structure is responsible for the irregular atrial rhythm during retrograde conduction in VFl and VF is uncertain. Unfortunately the lack of His bundle electrograms (hidden by VFl or VF waves) made it impossible to know the site of retrograde block: the His-Purkinje system, the AV node or both. This will require further investigation.

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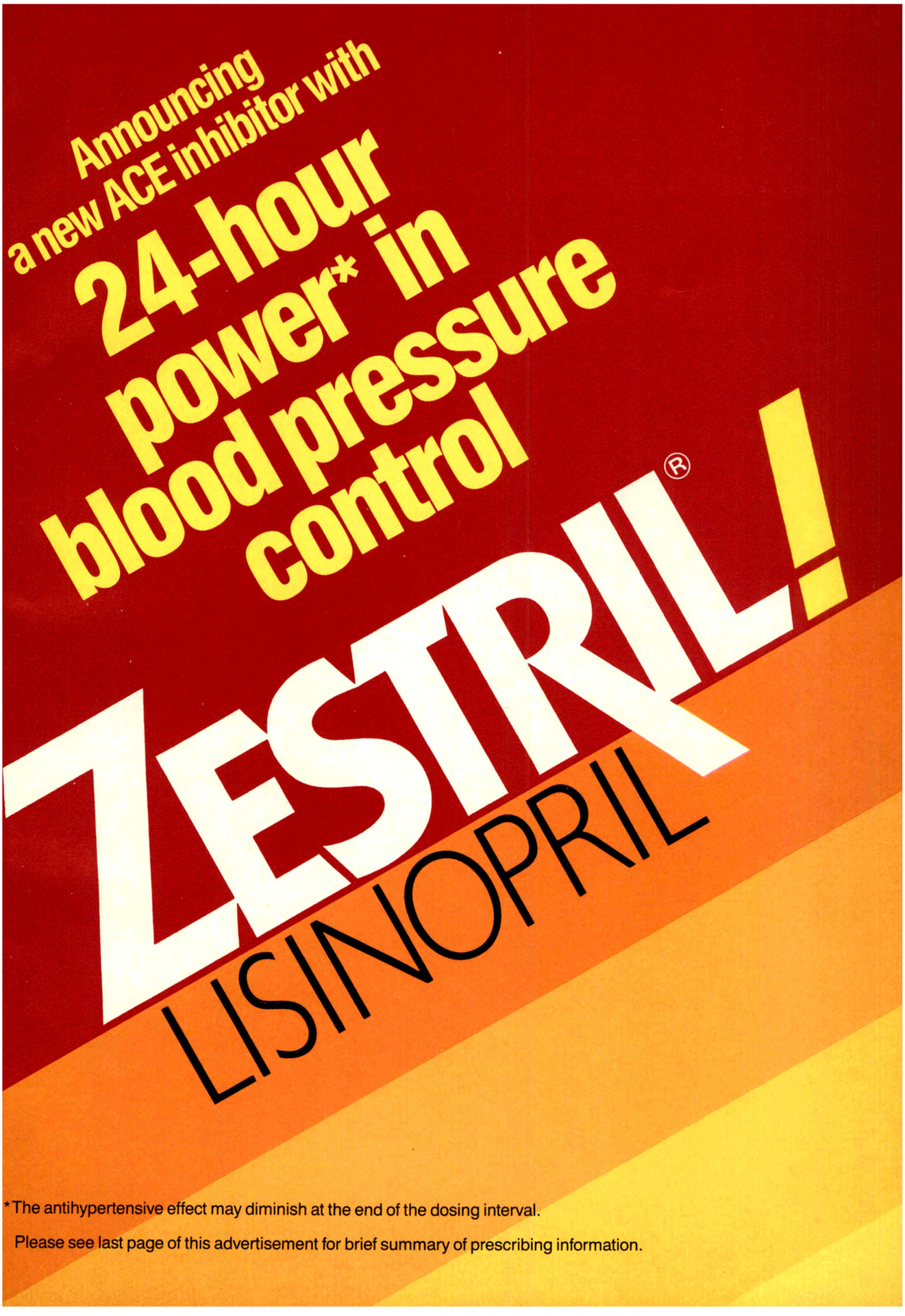
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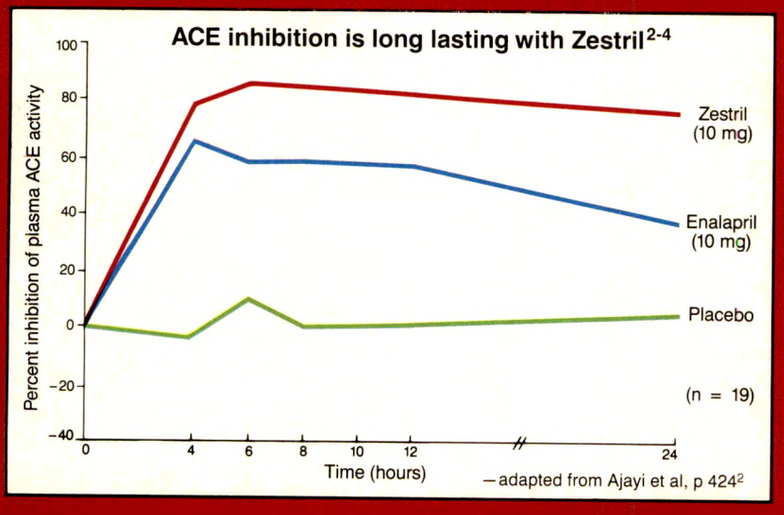
Zestril: The long-acting ACE inhibitor

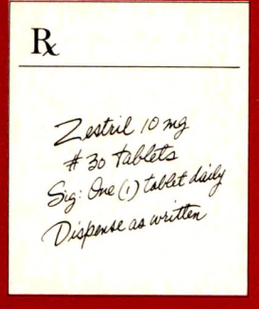
Zestril achieves 24-hour blood pressure control with a half-life of 12 hours.[1] Angiotensin converting enzyme (ACE) inhibition** is long lasting with Zestril—sustained 24 hours after a single dose.[2-4] The clinical significance of pharmacodynamic differences in hypertensive patients has not been determined.



** In pharmacodynamic studies (utilizing 10 mg of enalapril and lisinopril), ACE inhibition was significantly correlated to plasma renin activity and fall in diastolic blood pressure in normal volunteers.

Zestril: Hypertensive patients start and stay at one tablet a day

A single tablet of Zestril controls blood pressure for a full 24 hours[1]—unlike other ACE inhibitors, which may have to be increased to b.i.d.[5] or t.i.d.[6] dosing in some patients. The predictable once-daily dosage of Zestril enhances patient compliance and cost-effectiveness.



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* The antihypertensive effect may diminish at the end of the dosing interval.

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In ACE inhibitors
24-hour power* that's easy to live with
New ZESTRIL®!
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Zestril: 24-hour blood pressure control without liver metabolism

Zestril provides 24-hour control. Zestril is not metabolized by the liver.[7] It does not require bioactivation[7]—as needed with prodrugs such as enalapril:**[5,7] Zestril is absorbed as an active drug.[1] Absorption is unaffected by food.[8]

Zestril: 24-hour blood pressure control that's well tolerated

Zestril achieves 24-hour control with a low incidence of side effects. Rash and/or taste disturbance are rarely seen with Zestril. In Zestril clinical trials, the most frequently reported side effects were as follows:

Side Effects	Zestril (n = 2,003‡)	—	Placebo (n = 207)
Dizziness	6.3%	—	1.9%
Headache	5.3%	—	1.9%
Fatigue	3.3%	—	1.0%
Diarrhea	3.2%	—	2.4%
Upper respiratory symptoms	3.0%	—	0.0%
Cough	2.9%	—	1.0%

‡Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

- Only 6% of patients discontinued therapy in controlled clinical trials.
- Symptomatic hypotension occurs infrequently (0.8%) in patients with normal renal function but is a possible consequence in salt/volume-depleted persons such as those treated vigorously with diuretics.
- Evaluation of the hypertensive patient should always include assessment of renal function. (See Dosage and Administration.)
- Angioedema has been reported with ACE inhibitors, including Zestril. (See Warnings.)

Zestril dosage in hypertension
Starting dose is 10 mg once a day. Usual dosage range for maintenance: 20 to 40 mg per day, administered in a single daily dose.

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**Clinical significance has not been determined in hypertensive patients.

*The antihypertensive effect may diminish at the end of the dosing interval.

Please see last page of this advertisement for brief summary of prescribing information.

INDICATIONS AND USAGE. Zestril is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents. In using Zestril, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that Zestril does not have a similar risk. (See WARNINGS.) **CONTRAINDICATIONS.** Zestril is contraindicated in patients who are hypersensitive to this product. **WARNINGS. Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including Zestril. In such cases, Zestril should be promptly discontinued, and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, eg, subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) should be promptly administered. (See ADVERSE REACTIONS.) Hypotension:** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of use with Zestril in salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of Zestril and/or diuretic is increased. Similar considerations apply to patients with ischemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. **Neutropenia/Agranulocytosis:** Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment especially if they also have a collagen vascular disease. Available data from clinical trials of Zestril are insufficient to show that Zestril does not cause agranulocytosis at similar rates. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered. **PRECAUTIONS. General. Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including Zestril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of Zestril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when Zestril has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of Zestril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.) Hyperkalemia:** In clinical trials hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 2.2% of hypertensive patients and 4.0% of patients with congestive heart failure. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in approximately 0.1% of hypertensive patients. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with Zestril. (See Drug Interactions.) **Surgery/Anesthesia:** In patients undergoing major surgery or during anesthesia with agents that produce hypotension, Zestril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion. **Information for Patients. Angioedema:** Angioedema, including laryngeal edema, may occur especially following the first dose of Zestril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician. **Symptomatic Hypotension:** Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patient should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with their physician. **Hyperkalemia:** Patients should be told not to use salt substitutes containing potassium without consulting their physician. **Neutropenia:** Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which may be a sign of neutropenia. **NOTE:** As with many other drugs, certain advice to patients being treated with Zestril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. **Drug Interactions. Hypotension – Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Zestril. The possibility of hypotensive effects with Zestril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Zestril. If it is necessary to continue the diuretic, initiate therapy with Zestril at a dose of 5 mg daily, and provide medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS, and DOSAGE AND ADMINISTRATION.) When a diuretic is added to the therapy of a patient receiving Zestril, an additional antihypertensive effect is usually observed. Studies with ACE inhibitors in combination with diuretics indicate that the dose of the ACE inhibitor can be reduced when it is given with a diuretic. (See DOSAGE AND ADMINISTRATION.) **Indomethacin:** In a study in 36 patients with mild to moderate hypertension where the antihypertensive effects of Zestril alone were compared to Zestril given concomitantly with indomethacin, the use of indomethacin was associated with a reduced effect, although the difference between the two regimens was not significant. **Other Agents:** Zestril has been used concomitantly with nitrates and/or digoxin without evidence of clinically significant adverse interactions. No clinically important pharmacokinetic interactions occurred when Zestril was used concomitantly with propranolol or hydrochlorothiazide. The presence of food in the stomach does not alter the bioavailability of Zestril. **Agents Increasing Serum Potassium:** Zestril attenuates potassium loss caused by thiazide-type diuretics. Use of Zestril with potassium-sparing diuretics (eg, spironolactone, triamterene or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. **Carcinogenesis, Mutagenesis, Impairment of Fertility.** There was no evidence of a tumorigenic effect when lisinopril was administered for 105 weeks to male and female rats at doses up to 90 mg/kg/day (about 56 times* the maximum recommended daily human dose) or when lisinopril was administered for 92 weeks to (male and female) mice at doses up to 135 mg/kg/day (about 84 times* the maximum recommended daily human dose). *Based on patient weight of 50 Kg. Lisinopril was not mutagenic in the Ames microbial mutagen test with or without metabolic activation. It was also negative in a forward mutation assay using Chinese hamster lung cells. Lisinopril did not produce single strand DNA breaks in an in vitro alkaline elution rat hepatocyte assay. In addition, lisinopril did not produce increases in chromosomal aberrations in an in vitro test in Chinese hamster ovary cells or in an in vivo study in mouse bone marrow. There were no adverse effects on reproductive performance in male and female rats treated with up to 300 mg/kg/day of lisinopril. **Pregnancy. Pregnancy Category C:** Lisinopril was not teratogenic in mice treated on days 6-15 of gestation with up to 1,000 mg/kg/day (625 times the maximum recommended human dose). There was an increase in fetal resorptions at doses down to 100 mg/kg; at doses of 1,000 mg/kg this was prevented by saline supplementation. There was no fetotoxicity or teratogenicity in rats treated with up to 300 mg/kg/day (188 times the maximum recommended dose) of lisinopril at days 6-17 of gestation. In rats receiving lisinopril from day 15 of gestation through day 21 postpartum, there was an increased incidence in pup deaths on days 2-7 postpartum and a lower average body weight of pups on day 21 postpartum. The increase in pup deaths and decrease in pup weight did not occur with maternal saline supplementation. Lisinopril, at doses up to 1 mg/kg/day, was not teratogenic when given throughout the organogenic period in saline supplemented rabbits. Saline supplementation (physiologic saline in place of tap water) was used to eliminate maternotoxic effects and enable evaluation of the teratogenic potential at the highest possible dosage level. The rabbit has been shown to be extremely sensitive to angiotensin converting enzyme inhibitors (captopril and enalapril) with maternal and fetotoxic effects apparent at or below the recommended therapeutic dosage levels in man. Fetotoxicity was demonstrated in rabbits by an increased incidence of fetal resorptions at a dose of lisinopril at 1 mg/kg/day and by an increased incidence of incomplete ossification at the lowest dose tested (0.1 mg/kg/day). By whole body autoradiography, radioactivity was found in the placenta following administration of labeled lisinopril to pregnant rats, but none was found in the fetuses. There are no adequate and well-controlled studies in pregnant women. Zestril should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** Milk of lactating rats contains radioactivity following administration of ^{14}C lisinopril. It is not known whether this drug is excreted in human milk.

ZESTRIL® (lisinopril)

Because many drugs are excreted in human milk, caution should be exercised when Zestril is given to a nursing mother. **Pediatric Use:** Safety and effectiveness in children have not been established. **ADVERSE REACTIONS.** Zestril has been found to be generally well tolerated in controlled clinical trials involving 2003 patients and subjects. The most frequent clinical adverse experiences in controlled trials were dizziness (6.3%), headache (5.3%), fatigue (3.3%), diarrhea (3.2%), upper respiratory symptoms (3.0%), and cough (2.9%), all of which were more frequent than in placebo-treated patients. For the most part, adverse experiences were mild and transient in nature. Discontinuation of therapy was required in 6.0% of patients. In clinical trials, the overall frequency of adverse experiences could not be related to total daily dosage within the recommended therapeutic dosage range. For adverse experiences which occurred in more than 1% of patients and subjects treated with Zestril or Zestril plus hydrochlorothiazide in controlled clinical trials, comparative incidence data are listed in the table below.

Percent of Patients in Controlled Studies

	Zestril (n = 2003†) Incidence (discontinuation)	Zestril/Hydrochlorothiazide (n = 644) Incidence (discontinuation)	Placebo (n = 207) Incidence
Dizziness	6.3 (0.6)	9.0 (0.9)	1.9
Headache	5.3 (0.2)	4.3 (0.5)	1.9
Fatigue	3.3 (0.2)	3.9 (0.5)	1.0
Diarrhea	3.2 (0.3)	2.6 (0.3)	2.4
Upper Respiratory Symptoms	3.0 (0.0)	4.5 (0.0)	0.0
Cough	2.9 (0.4)	4.5 (0.8)	1.0
Nausea	2.3 (0.3)	2.5 (0.2)	2.4
Hypotension	1.8 (0.8)	1.6 (0.5)	0.5
Rash	1.5 (0.4)	1.6 (0.2)	0.5
Orthostatic Effects	1.4 (0.0)	3.4 (0.2)	1.0
Asthenia	1.3 (0.4)	2.0 (0.2)	1.0
Chest Pain	1.3 (0.1)	1.2 (0.2)	1.4
Vomiting	1.3 (0.2)	1.4 (0.0)	0.5
Dyspnea	1.1 (0.0)	0.5 (0.2)	1.4
Dyspepsia	1.0 (0.0)	1.9 (0.0)	0.0
Paresthesia	0.8 (0.0)	2.0 (0.2)	0.0
Impotence	0.7 (0.2)	1.6 (0.3)	0.0
Muscle Cramps	0.6 (0.0)	2.8 (0.6)	0.5
Back Pain	0.5 (0.0)	1.1 (0.0)	1.4
Nasal Congestion	0.3 (0.0)	1.2 (0.0)	0.0
Decreased Libido	0.2 (0.1)	1.2 (0.0)	0.0
Vertigo	0.1 (0.0)	1.1 (0.2)	0.0

†Includes 420 patients treated for congestive heart failure who were receiving concomitant digitalis and/or diuretic therapy.

Clinical adverse experiences occurring in 0.3% to 1.0% of patients in the controlled trials and rarer, serious, possibly drug related events reported in uncontrolled studies or marketing experience included: BODY AS A WHOLE: Chest discomfort, fever, flushing. CARDIOVASCULAR: Angina pectoris, orthostatic hypotension, rhythm disturbances, tachycardia, peripheral edema, palpitation. DIGESTIVE: Abdominal pain, anorexia, constipation, flatulence. METABOLISM: Gout. MUSCULOSKELETAL: Joint pain, shoulder pain. NERVOUS SYSTEM/PSYCHIATRIC: Depression, somnolence, insomnia, stroke. RESPIRATORY SYSTEM: Bronchitis, sinusitis, pharyngeal pain. UROGENITAL: Oliguria, progressive azotemia, acute renal failure. OTHER: Blurred vision, pruritus, urinary tract infection, vasculitis of the legs. ANGIOEDEMA: Angioedema has been reported in patients receiving Zestril (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with Zestril should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.) HYPOTENSION: In hypertensive patients, hypotension occurred in 1.2% and syncope occurred in 0.1% of patients. Hypotension or syncope was a cause of discontinuation of therapy in 0.5% of hypertensive patients. (See WARNINGS.) In patients with congestive heart failure, hypotension occurred in 5.0% and syncope occurred in 1.0% of patients. These adverse experiences were causes for discontinuation of therapy in 1.3% of these patients. **Clinical Laboratory Test Findings. Serum Electrolytes:** Hyperkalemia (See PRECAUTIONS.) **Creatinine, Blood Urea Nitrogen:** Minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 2.0% of patients with essential hypertension treated with Zestril alone. Increases were more common in patients receiving concomitant diuretics and in patients with renal artery stenosis. (See PRECAUTIONS.) Reversible minor increases in blood urea nitrogen and serum creatinine were observed in approximately 9.1% of patients with congestive heart failure on concomitant diuretic therapy. Frequently, these abnormalities resolved when the dosage of the diuretic was decreased. **Hemoglobin and Hematocrit:** Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.4 g% and 1.3 vol%, respectively) occurred frequently in patients treated with Zestril but were rarely of clinical importance in patients without some other cause of anemia. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. **Other (Causal Relationship Unknown):** Rarely, elevations of liver enzymes and/or serum bilirubin have occurred. Overall, 2.0% of patients discontinued therapy due to laboratory adverse experiences, principally elevations in blood urea nitrogen (0.6%), serum creatinine (0.5%), and serum potassium (0.4%). **OVERDOSAGE.** The oral LD_{50} of lisinopril is greater than 20 g/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of normal saline solution. **DOSAGE AND ADMINISTRATION. Initial Therapy:** In patients with uncomplicated essential hypertension not on diuretic therapy, the recommended initial dose is 10 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 20-40 mg per day administered in a single daily dose. The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with a dose of 10 mg daily. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, an increase in dose should be considered. Doses up to 80 mg have been used but do not appear to give greater effect. If blood pressure is not controlled with Zestril alone, a low dose of a diuretic may be added. Hydrochlorothiazide, 12.5 mg has been shown to provide an additive effect. After the addition of a diuretic, it may be possible to reduce the dose of Zestril. **Diuretic Treated Patients:** In hypertensive patients who are currently being treated with a diuretic, symptomatic hypotension may occur occasionally following the initial dose of Zestril. The diuretic should be discontinued, if possible, for two or three days before beginning therapy with Zestril to reduce the likelihood of hypotension. (See WARNINGS.) The dosage of Zestril should be adjusted according to blood pressure response. If the patient's blood pressure is not controlled with Zestril alone, diuretic therapy may be resumed as described above. If the diuretic cannot be discontinued, an initial dose of 5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) Concomitant administration of Zestril with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.) **Use in Elderly:** In general, blood pressure response and adverse experiences were similar in younger and older patients given similar doses of Zestril. Pharmacokinetic studies, however, indicate that maximum blood levels and area under the plasma concentration time curve (AUC) are doubled in older patients so that dosage adjustments should be made with particular caution. **Dosage Adjustment in Renal Impairment:** The usual dose of Zestril (10 mg) is recommended for patients with creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance > 10 mL/min ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 5 mg once daily. For patients with creatinine clearance < 10 mL/min (usually on hemodialysis) the recommended initial dose is 2.5 mg. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Renal Status	Creatinine-Clearance mL/min	Initial Dose mg/day
Normal Renal Function to Mild Impairment	>30	10
Moderate to Severe Impairment	≥10 ≤30	5
Dialysis Patients	<10	2.5‡

‡Dosage or dosing interval should be adjusted depending on the blood pressure response. Rev E 12/87

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Fatal and Nonfatal Cardiac Arrest in Patients with an Implanted Antitachycardia Device for the Treatment of Supraventricular Tachycardia

CHU PAK LAU, MB, MRCP
ELIZABETH CORNU
A. JOHN CAMM, MD, FRCP

Paroxysmal supraventricular tachycardia (SVT) is a frequent and disabling condition, sometimes unresponsive to medical therapy.[1] Tachycardia termination pacing is a useful alternative treatment in patients with SVT. The use of antitachycardia pacing has been shown to have acceptable long-term efficacy.[2] However, in patients with ventricular tachycardia it is known to carry a risk of tachycardia acceleration[3] or induction of ventricular fibrillation.[4] Therefore, for the treatment of ventricular tachycardia it is recommended that such pacemakers be physician activated (a manual nonautomatic mode) or used in association with an automatic implantable defibrillator.[5] The potential danger of tachycardia termination pacing for SVT is less well defined. We report 4 cases of fatal and 1 case of nonfatal cardiac arrest in patients fitted with an antitachycardia pacemaker, the Programmable Automatic Scanning Arrhythmia Reversion (PASAR) pacemaker (model 4151).

The data were collected in the form of questionnaires filled out by implanting physicians and returned to the pacemaker manufacturer (Telectronics). On a worldwide basis, a total of 122 patients (139 devices) had been implanted for the control of SVT. The follow-up period was 4 to 65 months (mean 34). Most patients (55%) had accessory pathways and 36% had atrioventricular nodal reentrant tachycardia. Sixty-one percent of the patients were paced from the right ventricular apex. Four cases of sudden unexplained cardiac deaths and 1 case of near sudden death were identified.

The PASAR model 4151 was a prototype, implantable, bipolar pulse generator that was designed to sense the occurrence of a tachycardia by programmable high rate criteria. After 4 consecutive tachycardia beats, 1 or 2 timed premature stimuli were delivered in an attempt to revert the tachycardia to sinus rhythm. How this device functions in tachycardia termination is shown in Figure 1. If tachycardia termination failed, the initial coupling interval between the last tachycardia cycle and the first stimulus was automatically decreased by 6 ms. This process could be repeated up to a maximum of 14 times. The coupling delay (between the first and second stimulus) was programmable but remained fixed as the first stimulus scanned the diastolic interval. The intervals successful in terminating tachycardia were stored so that when tachycardia was next confirmed, initial stimulation occurred at these intervals.

The clinical characteristics of the 4 patients who died suddenly are listed in Table I. Patient 1 was a 9-year-old girl who had dilated cardiomyopathy and SVT resistant to drug therapy. Electrophysiologic study showed the tachycardia to be due to intranodal reentry, and preexcitation was due to a nodoventricular (Mahaim) fiber that did not form a part of the tachycardia substrate (bystander). She also had congestive heart failure. Despite very frequent tachycardias (>50 episodes daily), the PASAR was considered the only possible treatment. Initially, the device performed satisfactorily, with effective control of all her arrhythmias. However, on the night before she was due to be discharged, she died suddenly. Figure 2 shows recordings from a Holter monitor and the possible causes of the arrhythmia at the time of her cardiac arrest. The most likely initiating event of ventricular fibrillation is the degeneration of an atrial arrhythmia into rapid atrial fibrillation during a tachycardia termination attempt by the PASAR. This had presumably conducted rapidly down the Mahaim fiber and resulted in ventricular fibrillation. A preimplantation electrophysiologic study had not documented this potential. There was also the possibility of inadvertent direct ventricular pacing by the proximal pole of the atrial wire, which may have prolapsed through the tricuspid valve and was possibly in contact with the ventricular endocardium. This might have accelerated the ventricular response by ventricular pacing during spontaneous tachycardia.

Patients 2 and 3 had Wolff-Parkinson-White syndrome with relatively short accessory pathway anterograde refractory periods (≤270 ms) and were paced from the right ventricle. Both had documented atrial fibrillation induced during electrophysiologic study with the shortest preexcited RR interval being 310 and 225 ms, respectively. Patient 2 had an 8-year history of palpitations requiring almost daily hospital visits. She had been perfectly well for the 11 months after the implantation of the PASAR. She had begun working as a newspaper delivery girl but collapsed while on her first delivery round. She had very recently discontinued therapy with β blockade. Patient 3, whose arrhythmia was satisfactorily controlled by the PASAR for over a year, died suddenly while reading a book without prior complaint of palpitation. In neither case was a cause of death identified at autopsy.

Patient 4 had atrioventricular nodal reentrant tachycardia. He also had ischemic heart disease and episodes of epigastric discomfort during tachycardia. The tachycardia was fully controlled by the PASAR. A 12-lead electrocardiogram showed an old inferior wall myocardial infarction and right bundle branch block. Holter monitoring had documented ventricular

From the Department of Cardiological Sciences, St. George's Hospital Medical School, Blackshaw Road, London SW17 0RE, England, and Telectronics, London, England.

Dr. Lau's present address: University Medical Unit, Queen Mary Hospital, Hong Kong. Manuscript received August 10, 1987; revised manuscript received December 7, 1987, and accepted December 8.

ectopic activity of >10 beats/hour. Atrial flutter was induced during electrophysiologic study with a ventricular response of 140 beats/min. Two weeks before sudden death, he had complained of an episode of dizziness but the electrocardiogram was unchanged. The electrode was implanted in the coronary sinus. He died suddenly while playing bowls without any complaint of chest pain or palpitation. No autopsy was performed.

A case of nonfatal cardiac arrest was documented in a 59-year-old woman with Wolff-Parkinson-White syndrome with a left-sided pathway. Electrophysiologic study showed atrioventricular reentrant tachycardia and atrial fibrillation, with a minimum preexcited RR interval of 155 ms. A temporary right ventricular wire was implanted in the right ventricular apex and over 80 successful attempts were made to terminate induced tachycardia by an external PASAR. A PASAR model 4151 was then implanted. In the first year she remained well. After 14 months she complained of more frequent palpitations and a Holter recording showed that appropriate pacemaker stimulation during a tachycardia termination attempt resulted in acceleration of tachycardia to a ventricular rate of more than 250 beats/min. This pacing system was immediately replaced by a PASAR model 4171 and an atrial electrode, and she has remained asymptomatic for the last 20 months.

Three of the 4 units from patients who died suddenly were recovered and returned to the manufacturer for testing. Two were operating close to the beginning of life and antitachycardia function was normal. The third unit was standard in all parameters but "auto-triggering" of the antitachycardia response by normal sinus rhythm was observed. This phenomenon has also been seen in some prototype units of the PASAR 4151 series, and implanting physicians had been appropriately informed. However, in this particular patient, several defibrillation attempts had been delivered during resuscitation and the auto-triggering might have been induced by this. Auto-triggering was not the cause of sudden death in patient 1 because the Holter recording near the time of death did demonstrate appropriate interventions by the pacemaker (Figure 2).

This report demonstrates a sudden death rate of 3% in this group of patients after a mean follow-up period of 34 months. Patients with SVT usually have a good prognosis, and sudden deaths are unusual but can oc-

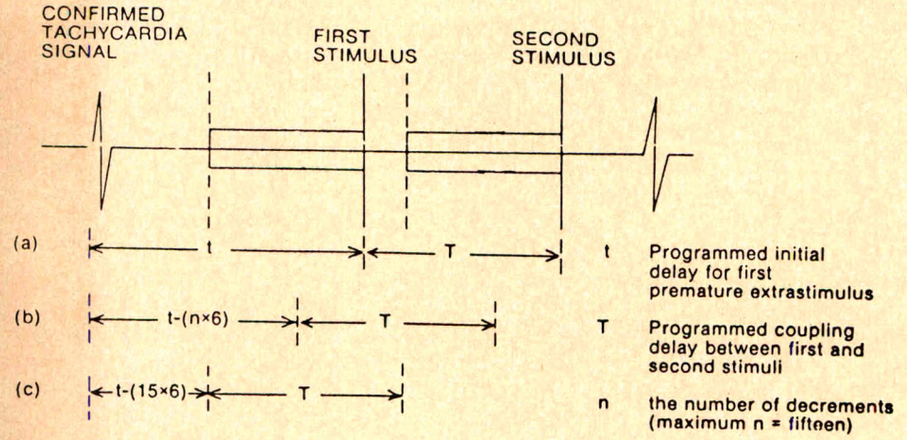

FIGURE 1. Tachycardia termination sequence of PASAR model 4151. The first and second stimuli were delivered at time *t* and *T*, respectively, after a sensed tachycardia. The coupling delay T remained fixed as the first stimulus is scanned through the diastole with 6-ms decrements. When a total of 15 attempts had occurred (*c*) the first stimulus returned to the initial delay (*t*) and the cycle was repeated.

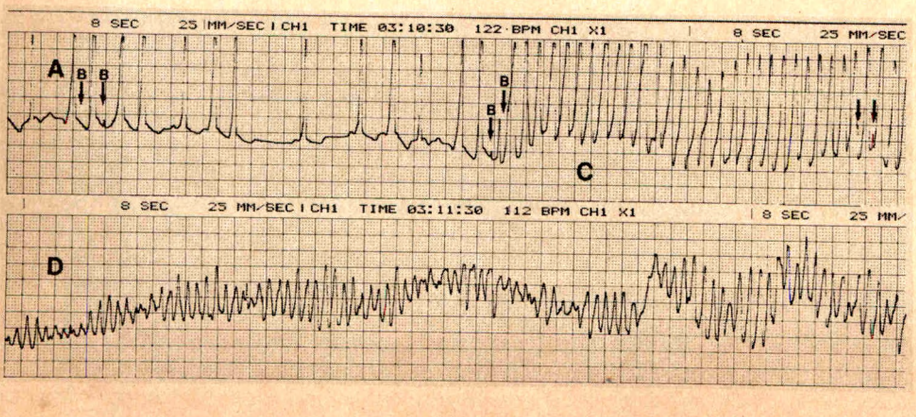

FIGURE 2. Holter recording of patient 1 at the time of sudden death. Possible explanations of the electrocardiographic recordings are listed as follows. *A* = spontaneous atrial tachyarrhythmia; *B* = PASAR stimulus artifacts emitted in response to spontaneous atrial arrhythmia resulting in atrial stimulation or ventricular stimulation; *C* = either atrial fibrillation with a rapid ventricular response due to PASAR-induced degeneration of atrial arrhythmia or spontaneous degeneration of atrial arrhythmia, or ventricular tachycardia due to inadvertant ventricular stimulation; *D* = ventricular fibrillation.

TABLE I Clinical Features of Four Patients Who Died Suddenly

Pt	Age (yrs), Sex	WPW	Anterograde Bypass ERP (ms)	SVT Type	SVT Rate	Pacing Site	Stimuli (n)	Heart Disease	Circumstances of Death	Follow-Up (mo)
1	9, F		Mahaim	AVRT	190	RA?	2	DC	Sudden (asleep)	1.5
2	13, F	A	270	AVRT	190	RV	2		Sudden (cycling)	11
3	52, F	A	260	AVRT	200	RV	2		Sudden (reading)	21
4	69, M		—	AVNRT	170	CS	2	CAD	Sudden (playing bowls)	13

AVNRT = atrioventricular nodal reentrant tachycardia; AVRT = atrioventricular reentrant tachycardia; CAD = ischemic heart disease; CS = coronary sinus; DC = dilated cardiomyopathy; ERP = effective refractory period; RA = right atrium; RV = right ventricle; SVT = supraventricular tachycardia.

cur in patients with the Wolff-Parkinson-White syndrome who develop atrial fibrillation. In a series reported by Gallagher et al,[6] 18 of a total of 163 patients with Wolff-Parkinson-White syndrome presented with ventricular fibrillation. However, most of these patients had an RR interval during preexcited atrial fibrillation of <205 ms, which was shorter than in those of our patients who died suddenly. Thus 4 cases of sudden death among 122 patients who received a PASAR is an unusually high mortality rate and raises the possibility of induction of lethal arrhythmias by the pacemaker.

Ventricular pacing has the danger of accelerating ventricular tachycardia.[3,4] Atrial fibrillation and nonsustained ventricular tachycardia have been documented during pacing attempts to terminate SVT.[7] The risk of inducing nonclinical arrhythmias is higher with multiple premature stimuli.[7] In the patient with nonfatal cardiac arrest ventricular tachycardia was induced when attempts were made to stop an SVT by ventricular pacing. The use of closely coupled double extrastimuli is thought to increase the risk of tachycardia acceleration. Patients 2 and 3 both had accessory pathways with short anterograde refractory periods (≤270 ms), and pacing stimuli were delivered in the right ventricle. Induction of ventricular tachycardia could be the responsible mechanism for sudden death. Alternatively, the extrastimuli might have provoked atrial fibrillation after conducting retrogradely to the atria.[7]

The Holter recording of patient 1 at the time of death illustrates degeneration of an atrial arrhythmia into ventricular fibrillation. Although the possibility of spontaneous degeneration cannot be excluded, inadvertent ventricular pacing could have been responsible. This might have resulted in ventricular tachycardia, especially if the pacing stimulus was delivered in the ventricular vulnerable period.

We have reported the potential danger of antitachycardia pacing for patients with SVT. Ventricular pacing, especially using closely coupled extrastimuli, should probably be avoided. Care should be taken in using this technique in patients with underlying heart disease. In patients with preexcitation syndromes with a short accessory pathway anterograde refractory period, pacing can result in atrial fibrillation with consequent rapid ventricular response. Tachycardia termination pacing should probably be avoided in this group of patients.

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Analysis of Antiarrhythmic Drug Concentrations Determined During Electrophysiologic Drug Testing in Patients with Inducible Tachycardias

NADA S. BERRY, PharmD
JERRY L. BAUMAN, PharmD
JOSE L. GALLASTEGUI, MD
WAYNE BAUMA, PharmD
KAREN J. BECKMAN, MD
ROBERT J. HARIMAN, MD

The approved type IA antiarrhythmic drugs quinidine, procainamide and disopyramide are widely used in the treatment of cardiac rhythm disturbances and serum concentrations of these drugs are frequently obtained. These drug levels are routinely interpreted in the context of commonly cited "therapeutic ranges" and used to guide therapy decisions and manipulate dosages. The present study was undertaken to evaluate the value of isolated serum concentrations of antiarrhythmic drugs and to analyze the effect of concentration on concordance and discordance of response.

The criteria for patient inclusion into the present study were: (1) symptomatic tachycardia requiring drug treatment, (2) control (drug free) and repeat (after drug therapy) electrophysiologic studies performed as clinically indicated and (3) serum drug concentration(s) determined during electrophysiologic drug testing. Between October 1978 and January 1987, 123 patients met these inclusion criteria and are the subject of this report. Data were compiled by a review of these patients' records. Of the 123 patients, 58 had paroxysmal supraventricular tachycardia (SVT) either due to atrioventricular (AV) nodal reentry or AV reentry incorporating an accessory AV connection, and the remaining 65 patients had ventricular tachycardia (VT). All patients had inducible sustained or symptomatic nonsustained SVT or VT during control electrophysiologic studies performed in the fasting, nonsedated state after all antiarrhythmic drugs had been discontinued for at least 5 elimination half-lives. The details of the stimulation protocol used in our laboratory for the induction of both SVT and VT have been reported elsewhere.[1-4]

Selection of a particular antiarrhythmic drug to be tested was based on the patient's history of response as well as any previous intolerable side effects noted. Patients were tested with quinidine (81 patients), procainamide (119) or disopyramide (44) in the following manner: quinidine 200 to 400 mg orally every 6 hours until presumed steady state; procainamide 1.0 to 1.5 g intravenously at 50 mg/min 30 minutes before programmed stimulation; and disopyramide 150 to 400 mg orally every 6 hours until presumed steady state. Initial dosages were selected based on patient-specific variables; lower amounts were used if concurrent diseases were suspected (e.g., coexisting liver disease, heart failure or renal disease). Serum for determination of antiarrhythmic drug concentrations was drawn in the postabsorptive (oral quinidine and disopyramide) or postdistributive (intravenous procainamide) state, at the time of the stimulation protocol. Serum concentrations were determined using the Syva EMIT assay. For the purposes of this study, the arbitrarily defined "therapeutic ranges" for these drugs were: quinidine 2 to 6 μg/ml; procainamide 6 to 12 μg/ml; and disopyramide 2 to 5 μg/ml. By definition, the antiarrhythmic drugs were well tolerated at the time of electrophysiologic testing and concentration sampling.

Patients were stratified into responders and nonresponders based on the results of electrophysiologic drug testing. Drug response was defined as inability to induce the tachycardia or induction of only brief (<15 beats) self-terminating SVT or VT not associated with symptoms.[5] If nonsustained tachycardia was induced during the drug-free control study, then patients were classified as responders only when the tachycardia was not inducible during drug testing. Nonresponse was defined as inducible SVT or VT that was unchanged from that induced during the control study. Concordance between the antiarrhythmic drugs was defined as the same result of electrophysiologic drug testing for all drug trials. Positive concordance was response to all drugs tested and negative concordance was no response to all drugs tested. Discordance resulted if there was a response to at least 1 of the drugs but nonresponse to at least 1 of the other agents.

Statistical analysis was performed by the Student t test for independent samples. Significance was deter-

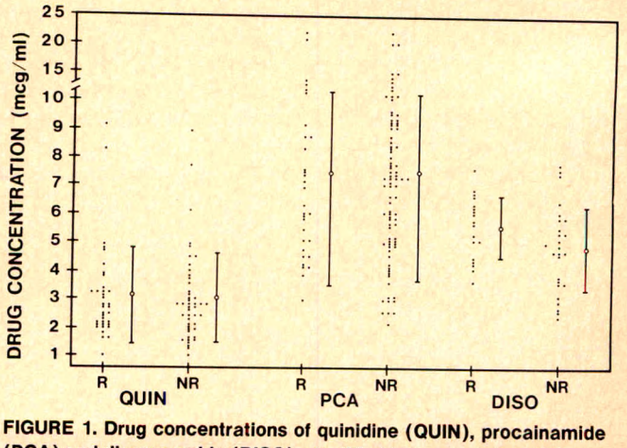

FIGURE 1. Drug concentrations of quinidine (QUIN), procainamide (PCA) and disopyramide (DISO), stratified into responders (R) and nonresponders (NR) in 123 patients. *Closed circles* represent individual drug concentrations. *Open circles* represent mean drug concentration and are illustrated to the *right* of each scatter plot; vertical bars represent standard deviation.

From the Departments of Pharmacy Practice and Medicine, Section of Cardiology, University of Illinois at Chicago, Chicago, Illinois 60612. Manuscript received October 13, 1987; revised manuscript received December 21, 1987, and accepted December 24.

mined at $p < 0.05$. All data were expressed as mean ± standard deviation.

The serum concentrations of the 3 antiarrhythmic drugs, independent of the type of tachycardia, were analyzed (Figure 1). In the 33 patients responding to quinidine the serum concentrations ranged from 1.0 to 9.1 (3.1 ± 1.7) μg/ml compared with 1.0 to 8.9 (3.0 ± 1.6) μg/ml for the 48 nonresponders (difference not significant). In those receiving procainamide, the 30 responders had serum concentrations ranging from 2.9 to 22.2 (7.4 ± 4.0) compared with 2.1 to 22.2 (7.4 ± 3.8) μg/ml in the 89 nonresponders (difference not significant). The 18 responders to disopyramide had serum concentrations ranging from 3.6 to 7.5 (5.5 ± 1.1) compared with 2.3 to 7.7 (4.7 ± 1.5) μg/ml for the 26 nonresponders (difference not significant). Of the 123 patients, 58 responded to at least 1 of the 3 agents; 16 patients (28%) had drug concentrations below the therapeutic range. Drug concentrations were further analyzed by stratifying the patients into those with SVT and those with VT (Table I).

Of the 123 patients, 83 were tested with multiple drugs and the effect of drug concentration on concordance and discordance was examined. Of these 83 patients, 26 had discordant and 57 had concordant responses. In the former group of 26 patients, 12 (46%) had drug concentration patterns that could explain the discordant responses (Figure 2). These 12 patients consisted of 4 responding to an antiarrhythmic associated with isolated high drug concentrations (above the therapeutic range) and 8 who did not respond to 1 of the drugs associated with an isolated low concentration (below the therapeutic range). The remaining 14 patients in this group displayed no pattern relating

TABLE I Serum Drug Concentrations (μg/ml) in Patients with Paroxysmal SVT or VT for Responders and Nonresponders

	No.	Range	Mean ± SD	p Value
Supraventricular tachycardia				
Q R	25	1.0–8.3	2.9 ± 1.4	NS
NR	13	1.3–8.9	3.5 ± 1.3	
P R	20	2.9–22.2	7.7 ± 4.6	NS
NR	36	2.5–14.8	6.6 ± 2.9	
D R	15	3.6–7.5	5.6 ± 1.2	NS
NR	11	2.3–7.7	4.5 ± 1.7	
Ventricular tachycardia				
Q R	8	2.0–9.1	3.9 ± 2.2	NS
NR	35	1.0–7.7	2.7 ± 1.3	
P R	10	4.1–11.8	6.9 ± 2.4	NS
NR	53	2.1–22.2	7.8 ± 4.3	
D R	3	4.2–5.6	5.0 ± 0.7	NS
NR	15	2.5–7.5	4.9 ± 1.4	

D = disopyramide; NR = nonresponders; NS = difference not significant; P = procainamide; Q = quinidine; R = responders; SD = standard deviation.

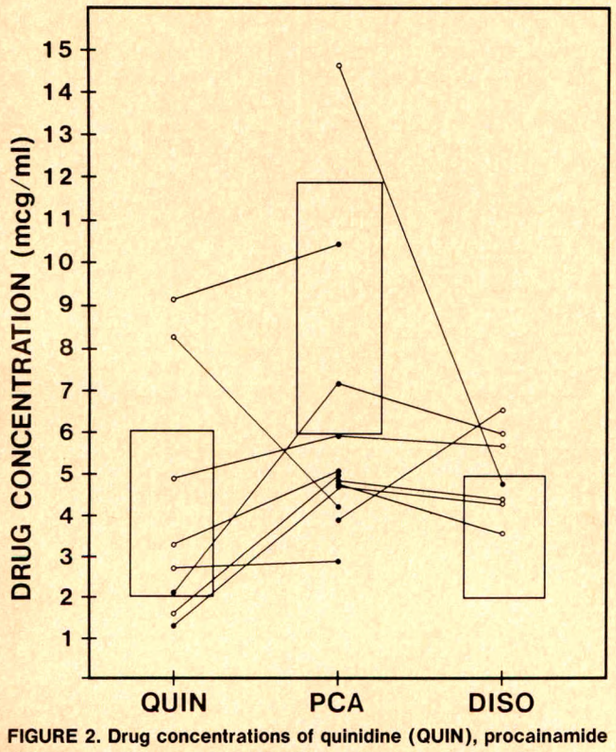

FIGURE 2. Drug concentrations of quinidine (QUIN), procainamide (PCA) and disopyramide (DISO) in 12 patients with discordant responses that could be explained by isolated high or low drug concentrations. *Closed circles* represent nonresponse, and *open circles* represent response. *Circles* are connected by lines to show individual patient responses at a specific concentration. *Boxed areas* represent the therapeutic ranges used.

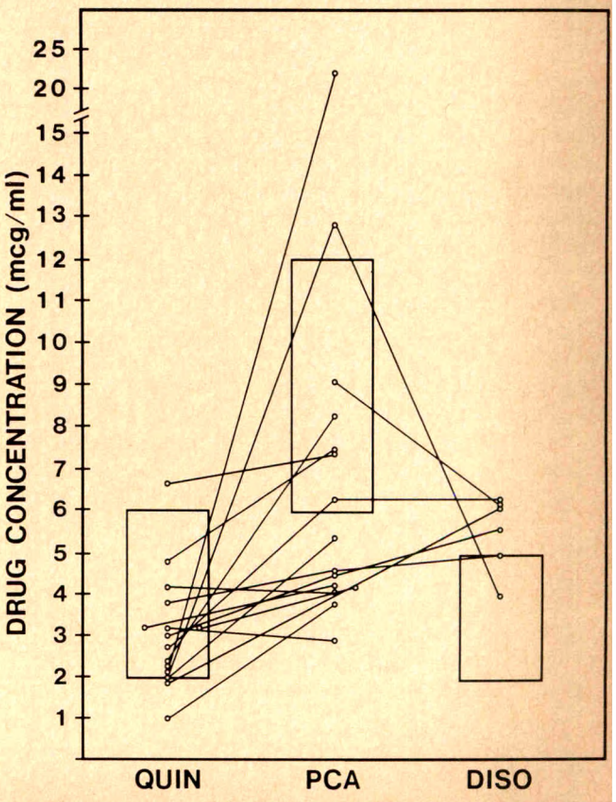

FIGURE 3. Drug concentrations of quinidine (QUIN), procainamide (PCA) and disopyramide (DISO) for 16 patients with positive concordance. Symbols as in Figure 2.

response to drug concentration; all serum levels were generally within the therapeutic range despite the observed discordant responses. In the group of 57 patients with concordance, 41 had negative concordant responses. The remaining 16 patients had positive concordance and 9 (56%) responded to an antiarrhythmic despite low concentrations of that agent (Figure 3).

These results indicate that the published therapeutic ranges of the type IA antiarrhythmic drugs should be used only as a rough guide to therapy and certainly not as any form of therapeutic endpoint. The mean effective concentrations in patients responding to therapy were virtually identical to the mean ineffective concentrations in patients not responding to these drugs. Also, the range of concentrations in which efficacy was demonstrated was extremely wide: procainamide 2.9 to 22.2 μg/ml and quinidine 1.0 to 8.9 μg/ml. When the data were analyzed separately for patients with SVT or VT, the results were similar. It is clear that one cannot differentiate responders from nonresponders solely on the basis of serum concentrations.

Because the type IA agents have similar electrophysiologic actions, some investigators have suggested a concordance of response for these drugs,[3,6] while others have found no concordance.[7,8] It is possible that differences in drug concentrations may account for some of the discrepancies in these findings. For this reason, we analyzed patients with discordant responses, searching for those with very high or low drug concentrations. Almost one-half of those patients with discordant responses had either isolated low drug concentrations (nonresponders) or isolated high drug concentrations (responders). Thus, it is possible that discordant responses are attributable to differences in drug concentrations in a significant number of patients. However, drug concentrations were also analyzed in a group displaying positive concordance. Similarly, about one-half of these patients had an isolated low concentration, yet were responders to that specific drug. This finding implies the opposite possibility, namely that response in some patients is relatively concentration insensitive. A likely explanation for these results is that a wide range of effective concentrations exists within a population of patients. This may be due to differences in the determinants and sensitivities of the reentrant circuit, differences in drug distribution to the site of the tachycardia or both. We believe there is a threshold concentration for effectiveness, but in a given patient, this threshold is highly variable and, at present, unpredictable.

Our electrophysiologic testing protocols have changed in the past decade to include the use of triple extrastimuli (but not left ventricular stimulation); it is possible that these procedural changes may have affected the results. Also, patients were not routinely retested if the serum concentration was low. Recently, Wyse et al[8] prospectively studied 32 patients with inducible VT after quinidine, procainamide and disopyramide therapy in both a low- and high-dose regimen. The high-dose regimen resulted in higher drug concentrations but did not appreciably improve response rate (particularly for quinidine and disopyramide). In reviewing our patients' records, 7 were retested at higher drug concentrations if nonresponse was observed at a low serum level. Of these 7 patients, only 1 responded at a higher concentration. It is therefore unlikely that the administration of several dosage regimens and retesting at various resultant serum concentrations would have caused the results to be dramatically different.

Although some patients display a concentration-dependent response to antiarrhythmic drug therapy, a significant number of patients seem to display a response that is relatively independent of drug concentration. Because of this and the observed high variability in effective concentrations, we offer the following guidelines when using serum concentrations of the antiarrhythmic drugs. When efficacy is demonstrated (by electrophysiologic testing or electrocardiographic monitoring), a serum concentration is determined at presumed steady state. Unless drug intolerance is encountered, this level then becomes the patient's therapeutic level and long-term oral administration is tailored to match the effective concentration. Commonly quoted therapeutic ranges are used only as rough guidelines and the effective concentration is specific for that patient's tachycardia.

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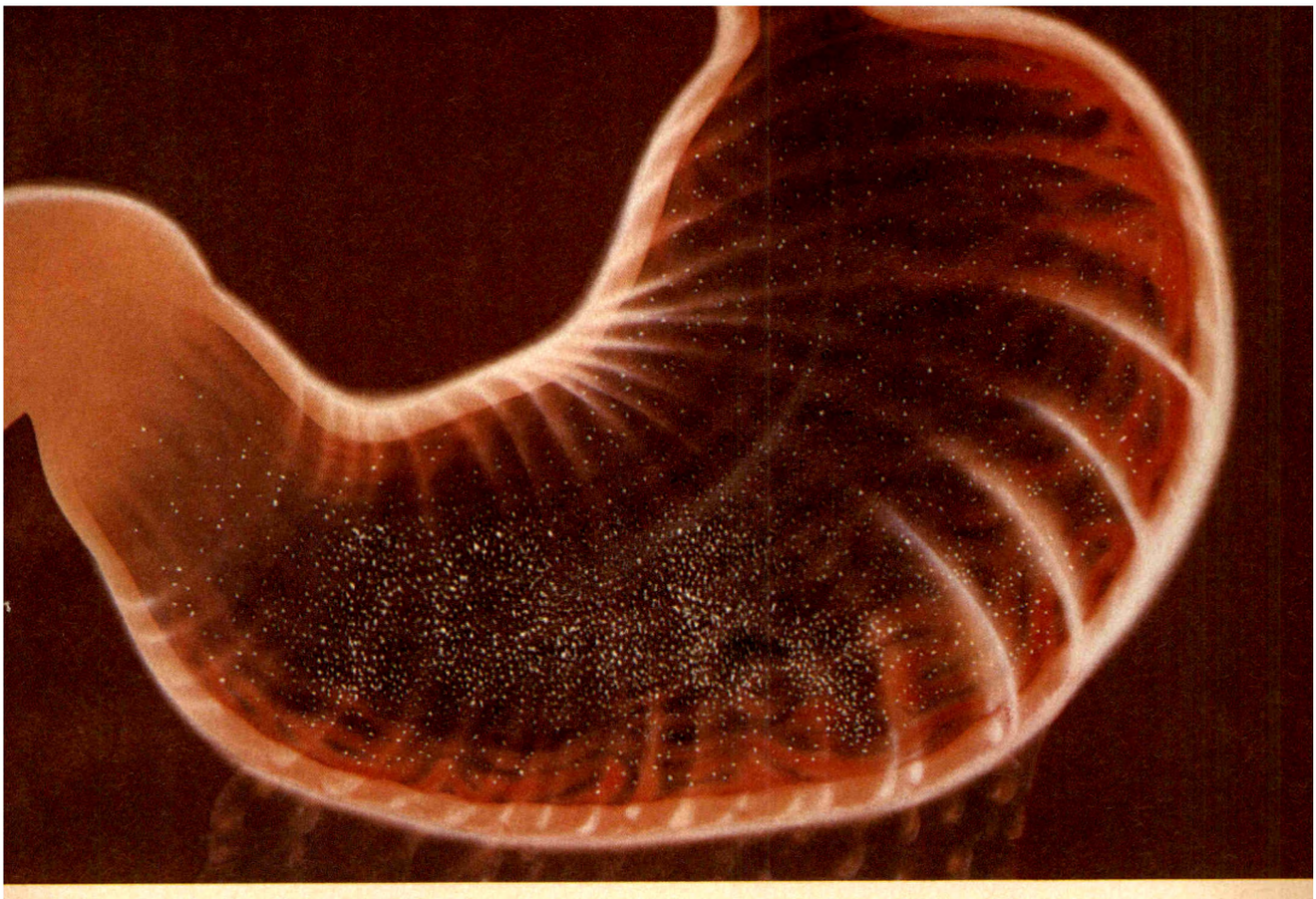

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Slow-K (n = 15)	t.i.d.	2	1
SR KCl Capsule (n = 15)	t.i.d.	0	2
Placebo (n = 15)	b.i.d.	0	4

Like a liquid, K-Dur 20 Microburst Release System is designed to disperse immediately. Minute, sustained action particles are distributed over a wide surface area. The potassium chloride is then slowly released. Rapid, wide dispersion followed by slow release of the potassium minimizes contact between the gastric mucosa and concentrated quantities of potassium chloride.[1]

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INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS.**

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE).** There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS);** other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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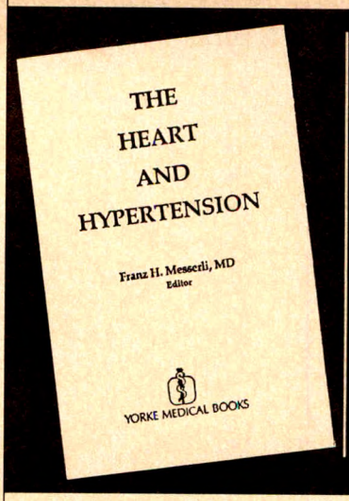

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Acute Termination of Supraventricular Tachyarrhythmias in Children by Transesophageal Atrial Pacing

MACDONALD DICK II, MD
WILLIAM A. SCOTT, MD
GERALD S. SERWER, MD
BURT I. BROMBERG, MD
ROBERT H. BEEKMAN, MD
ALBERT P. ROCCHINI, MD
A. REBECCA SNIDER, MD
DENNIS C. CROWLEY, MD
AMNON ROSENTHAL, MD

Supraventricular tachyarrhythmia, in contrast to arrhythmias in adults, is the most common abnormal tachycardia in infants and children.[1] When the tachyarrhythmia is reentrant, conversion by physiologic, pharmacologic or electrical interruption of conduction within a limb of the circuit is highly probable. Manipulation of physiologic vagal tone, the obviously preferred mode, is not successful or feasible in a number of patients. Pharmacologic manipulation has been the most commonly used; however, digoxin and propranolol may require several hours for conversion. Intravenous administration of verapamil offers prompt termination[2,3]; however, in newborns it may be unsuccessful and carries the risk of hypotension, bradycardia, apnea and negative inotropy, especially in patients with coexisting congestive heart failure.[4] Electrical conversion by transvenous atrial pacing or by direct current cardioversion requires invasive entry for 1 technique and frequently general anesthesia for the other. Recent reports from our institution[5-7] as well as from others[8,9] have demonstrated the usefulness, simplicity and safety of transesophageal atrial burst pacing for conversion of reentrant tachyarrhythmias in infants and children. The technique, however, has not been included among the recent recommendations of several authorities.[10-12] Our purpose, therefore, is to report our experience with transesophageal pacing in infants and children so that the technique may be more widely known.

Between April 15, 1983, and December 31, 1986, 43 children (25 boys and 18 girls) seen at our institution experienced 73 episodes of supraventricular tachyarrhythmia. Three of these children were less than 1 week of age; 7 children were 1 to 4 weeks of age; 9 were 1 to 12 months of age; 13 were 1 to 10 years of age; and 11 were 10 years of age at the time of their initial episode. Among the 43 patients, 25 had no structural heart disease; 18 had associated postoperative heart disease (9 transposition of the great arteries, 3 univentricular heart and 1 each of 6 different lesions). The older children were symptomatic with palpitations and the infants were symptomatic with tachypnea; 1 infant had hydrops. Twenty-six children had supraventricular tachycardia (SVT) and 17 had atrial flutter. For the purposes of this study, SVT was defined as narrow QRS tachycardia (except in patients in whom preexisting bundle branch block was known), and by history or observation of abrupt initiation and termination and retrograde P waves with short RP intervals.

Atrial flutter was defined by typical sawtooth-pattern P waves and variable atrioventricular block (leads II, III, aVF, V_1) on the electrocardiogram. Following the Mustard or Fontan operation, because of slow intraatrial conduction, the typical pattern is frequently absent in such patients. Atrial flutter in this group of patients was considered present if variable atrioventricular block was observed during the tachycardia and history or observation of abrupt initiation and termination was present. Of the 26 children with SVT, only 2 had associated structural heart disease; in contrast, 14 of the 17 children with atrial flutter had structural heart disease. Among the 25 children with SVT, 10 had preexcitation. Four patients, including 2 infants, were converted from 6 different episodes as outpatients, avoiding hospitalization. In addition 4 patients were converted after surgery while still in the intensive care unit.

To begin transesophageal pacing the patient is first connected to a 3-lead standard electrogram. An intravenous line is not routinely placed. The choice of the electrode catheter depends on the patient's age and size. In infants and small children up to 2 to 3 years of

TABLE I Clinical and Electrophysiologic Data

	No.	Mean ± SD	Range
Age (yr)			
Initial episode	43	5 ± 6	1 day–19 yr
Weight (kg)	43	—	2–77
Height (cm)	43	—	46–170
Arrhythmia (episode)			
Cycle length (ms)			
Supraventricular tachycardia	43	236 ± 46	140–333
Atrial flutter	27	241 ± 51	160–350
Pacing cycle at converison length (ms)			
Supraventricular tachycardia (episodes)	44	188 ± 36	100–300
Atrial flutter (episodes)	26	170 ± 34	110–220
Pacing stimulus strength at threshold (capture)			
Supraventricular tachycardia			
Amplitude (mA)	43	14 ± 4	8–20
Pulse duration (ms)	43	5 ± 2	3–10
Atrial flutter			
Amplitude (mA)	26	16 ± 3	10–20
Pulse duration (ms)	26	6 ± 2	4–10

The descrepancy in numbers between the arrhythmia and the pacing cycle length is related to incomplete data in a few patients.

From the Division of Pediatric Cardiology, C.S. Mott Children's Hospital, and the Department of Pediatrics, University of Michigan, Ann Arbor, Michigan. Manuscript received October 15, 1987; revised manuscript received and accepted December 11, 1987.

age, a 4Fr bipolar (10 mm interelectrode distance) catheter is used (n = 49 episodes). For children 3 to 8 years of age, a 6Fr endocardial pacing catheter (interelectrode distance 2.9 cm) is used (n = 13). Children 8 years and older are asked to swallow an electrode "pill" (n = 11). The 2 electrodes of the bipolar catheter are then connected to a recording amplifier and strip chart recorder. The electrodes are positioned close to the atrium by identifying the maximal atrial electrogram, thus enhancing the atrial signal, which may be small or within the QRS complex on the electrocardiogram. The battery powered stimulator provides constant current pulses from 1 to 40 mA and 1 to 10 ms in impulse amplitude and duration, respectively (Arzco Inc.). However, because of the experience in adults of excessive esophageal discomfort at stimulus strengths of >20 mA current and >10 ms pulse duration, no attempt to pace patients at outputs in excess of those values is made. The threshold is measured at the minimal current and pulse duration required for constant atrial capture (Table I). Pacing is delivered in bursts of 3 to 10 seconds at 90% of the tachyarrhythmia cycle length, reducing the cycle length of each burst by 10 ms until either the arrhythmia is converted or refractoriness of the atria is reached. Details of the technique have been published previously.[5-7] Other than one 18-month-old infant, no children under 2 years of age received sedation. Children aged 2 to 12 years often expressed apprehension regarding passage of the electrode catheter. In the 10 patients with continuing apprehension, sedation was accomplished with 75 to 100 mg/kg of chloral hydrate by mouth, an intramuscular injection (1 patient) of meperidine (1 mg/kg), phenergan (0.5 mg/kg) and thorazine (0.5 mg/kg), or diazepam (1 to 5 mg) administered intravenously. Because swallowing the pill electrode requires an awake, cooperative state, the 11 children using the pill did not receive (or request) sedation.

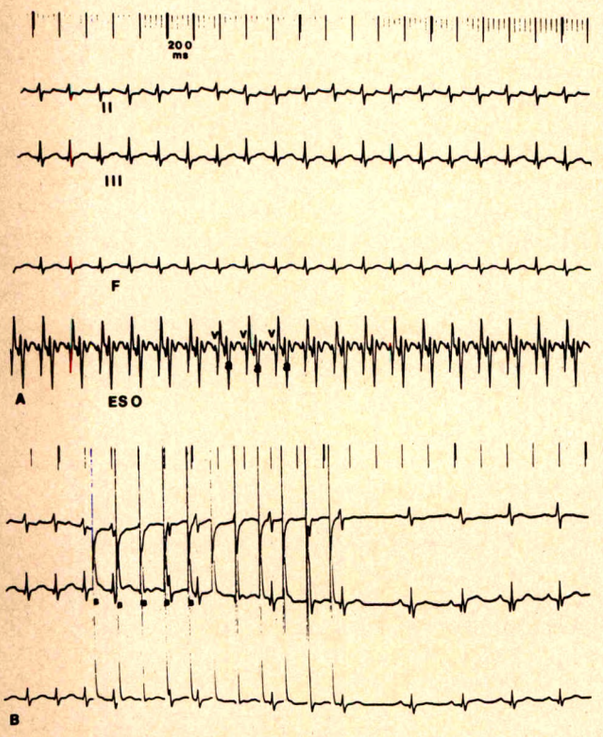

FIGURE 1. *A*, 3 surface electrocardiographic leads (II, III, F) and simultaneous esophageal lead (ESO) demonstrating tachycardia at a heart rate of 273 beats/min (cycle length 220 ms) in a 1-month-old infant. Note the narrow QRS and the large atrial (a) electrogram equal to the ventricular (v) electrogram. *B*, pacing stimuli (s) are delivered at a cyclic length of 170 ms (353 beats/min) for 1.7 seconds. Normal sinus rhythm appears after termination of pacing.

The threshold could be determined in each patient before conversion. Ninety-one percent (42/46) of episodes of supraventricular tachycardia were successfully converted using this technique (Figure 1). In contrast 74% (20/27) of episodes of atrial flutter were successfully converted to sinus rhythm ($p = 0.06$). Reasons for failure in the SVT group include failure to achieve capture in one 13-year-old patient dispite maximal 20 mA and 10 ms stimulus strength, depleted stimulator battery in 2 infants with SVT and insufficient shortening of the pacing cycle length in the fourth. All these failures occurred early in our experience (within the first 25 trials) and most likely can be avoided by improved attention to technique. Reason for failure of conversion of atrial flutter by this technique has been reviewed previously.[6] Conversion of SVT was achieved with pacing cycle length of 78% of the SVT cycle length. The pacing cycle length required to convert the patients with atrial flutter was slightly shorter at 71% of the atrial flutter cycle length. The threshold for capture was not related to the patients' age or size, the catheter used or the tachyarrhythmia converted, and did not differ between 2 separate episodes of tachyarrhythmia within a single patient with multiple episodes. Likewise, successful conversion was not related to the presence or absence of heart disease either as a whole or within either tachyarrhythmia groups[5-7] or to the presnce or absence of concurrent digoxin therapy.

All verbally expressive children stated, when asked, that they felt a sensation of "heartburn" (substernal discomfort) with each pacing discharge.[5-7] In no patient did this sensation require termination of the procedure. No complications were noted in the infants and children in whom the 4Fr soft bipolar electrode catheter was used. Passage of the catheter into the trachea occurred in a 13-year-old girl at which point the catheter was withdrawn and correctly placed with successful conversion. One 15-year-old girl bit through the fine wire of the pill electrode resulting in inadvertent pacing of her tongue. The pill was withdrawn, and exchanged for an endocardial pacing catheter with successful conversion. The next day she required repeat conversion and the pill was used successfully. One 19-year-old girl with a dual chamber pacemaker required programming of the pacemaker to the asynchronous (fixed rate) ventricular mode during conversion of atrial flutter to avoid inhibition of the pacemaker and ventricular asystole. One 5-year-old boy experienced inadvertent intermittent ventricular pacing during an unsuccessful at-

tempt in converting atrial flutter; no adverse effect was noted. Two 17-year-old boys immediately regurgitated the pill electrode after swallowing (they are not included in the 43 study patients).

Arrhythmias generated as a result of the technique occurred in 8 patients, all with atrial flutter. Three patients (2 with transposition/Mustard) were converted from atrial flutter to atrial fibrillation; the fibrillation persisted from 30 seconds to 45 minutes before self-extinguishing into sinus or a stable junctional rhythm. Three patients, all with transposition/Mustard, were converted from atrial flutter to atrial fibrillation or a faster flutter; these patients then received transthoracic direct current cardioversion under general anesthesia. No patient experienced hemodynamic deterioration or a ventricular response during atrial fibrillation faster than that observed during the original 2:1 atrioventricular block of atrial flutter. One patient with preexcitation but in atrial flutter was converted to SVT; the latter tachycardia was immediately converted to sinus rhythm. The final patient is the one with inadvertent ventricular pacing; no sustained arrhythmia was initiated. Thus, in none of the patients did an adverse arrhythmia develop and, importantly, in 3 patients conversion to a stable rhythm was achieved by a transition through a period of nonsustained atrial fibrillation.

These data indicate that transesophageal atrial pacing easily, predictably and safely converts reentrant supraventricular tachyarrhythmias to normal sinus rhythm. Although we and others have reported similar pediatric experience previously,[5-9] this more comprehensive serial study underscores the usefulness and safety of this technique especially in infants. Many authorities suggest that the first-line therapy for supraventricular tachycardia in infants and children is digoxin, and that if the patient is hemodynamically impaired, transthoracic direct current cardioversion.[10-12] Our data indicate that the delay inherent in digoxin or propranolol therapy, the risk of intravenous verapamil therapy and the transthoracic electrical discharge often requiring general anesthesia can frequently be avoided by transesophageal atrial pacing.

Our experience outlines several special applications of this technique in the young. First, although the time required to achieve access to the atria through the transesophageal route was not recorded, passage of the nasoesophageal catheter appeared to be quicker, simpler and less traumatic in an infant than establishing an intravenous route for pharmacologic agents. This difference in access is heightened by the potentially deleterious response to intravenous verapamil in the infant. Second, the use of a pill electrode requires, and may even encourage, a cooperative, participatory attitude in a reluctant older child or adolescent. The youngest patient to swallow the pill, which was used in all patients older than 10 years, was 8 years old. Third, the successful conversion of 74% of atrial flutter episodes suggests that this technique—perhaps because of the theoretical advantage of overdrive pacing for intraatrial reentrant arrhythmias when compared with most antiarrhythmic agents, and the smaller atrial size of young subjects—may be particularly suitable for children with atrial flutter.[6] Finally these data address the role of transesophageal atrial pacing in conversion of repeated episodes of either supraventricular tachycardia or atrial flutter in a single patient. Clearly, burst pacing through any route is an acute therapeutic technique and not a prophylactic one. Yet only 1 infant and two 8-year-old girls who were easily converted by transesophageal pacing immediately (within seconds) resumed the tachycardia. On the other hand, 19 of the 43 children required 1 or more repeat conversions at an interval of several hours to 3 years. Importantly, 4 of the 10 infants required repeat converison during their initial hospitalization while drug treatment was under evaluation. Although this study did not randomly assign to the patient episode or type of SVT transesophageal atrial pacing, drug trials or direct current cardioversion, it is nonetheless clear that atrial pacing through the esophagus offers at least equally prompt and safe therapy compared with the other forms of converison, especially in the infant.

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Color and Pulsed-Wave Doppler Study of Aortic Regurgitation in Systemic Hypertension

CARLO VIGNA, MD
ALDO RUSSO, MD
MAURO PELLEGRINO SALVATORI, MD
FRANCESCO LAURENZI, MD
GIANPIERO PERNA, MD
ALESSANDRO VILLELLA, MD
TOMMASO LANGIALONGA, MD
RAFFAELE FANELLI, MD
FRANCESCO LOPERFIDO, MD

Aortic regurgitation (AR) has been found with varying frequency in patients with systemic hypertension (SH).[1] The degree of AR in this clinical setting is usually mild.[2,3] Although it has been suggested that AR occurs in patients with SH as a consequence of the anatomic changes of aortic cusps, which are in turn related to both duration and severity of SH,[3] no recent study has investigated this.

From January to June 1987, we studied 98 consecutive patients with stable SH, 52 male and 46 female, mean age 56 ± 14 years, by color and pulsed-wave Doppler. Each patient had had SH for at least 3 years and had been diagnosed according to World Health Organization criteria. Patients referred for aortic valve disease (regurgitation or stenosis) were excluded from the study. Twenty-seven healthy normotensive subjects, 15 male and 12 female, mean age 57 ± 14 years, constituted the control group. Two-dimensional echocardiographic and Doppler studies were obtained using the Aloka SDS 860 color Doppler system, with 2.5- and 3.5-MHz transducers, by 2 observers unaware of clinical findings. AR was classified as mild and more than mild, according to whether diastolic regurgitant turbulence in both long-axis parasternal and 4-chamber or right anterior equivalent apical views[4] extended only to left ventricular outflow tract or further into the left ventricle (Figure 1A). Diastolic turbulence below the aortic cusps was considered suggestive of AR if it lasted the whole diastole, as confirmed by pulsed-wave Doppler analysis (Figure 1B).[5] Doppler findings were related to the following clinical data: length of history of SH and highest measurements of systolic and diastolic blood pressure, as reported by patient's physician; systolic and diastolic blood pressure and audibility of AR diastolic murmur at the time of Doppler studies. The following 2-dimensional echocardiographic data were considered: aortic anulus size, aortic root size and aortic cusp thickening (1 or more normally motile echo-dense leaflets). Concentric left ventricular hypertrophy was considered to be present if both left ventricular posterior wall and ventricular septum thickness exceeded 12 mm. Isolated hypertrophy of ventricular septum, which may occur in patients with SH,[6] was also noted.

AR was found in 37 of 98 patients with SH (38%) and 3 of 27 control subjects (11%) ($p < 0.001$). AR was

From the Department of Cardiology, Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, and the Institute of Cardiology, Universita' Cattolica del Sacro Cuore, Roma, Italy.
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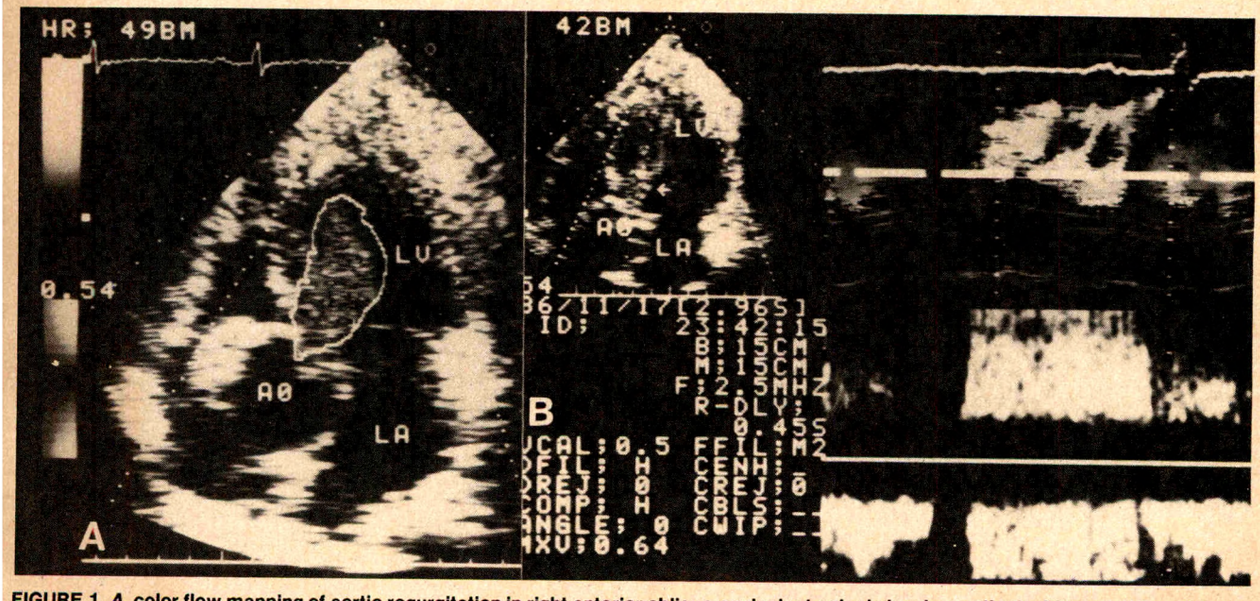

FIGURE 1. ***A*, color flow mapping of aortic regurgitation in right anterior oblique equivalent apical view in a patient with more than mild systemic hypertension (extension of AR jet is shown by the computer mark).** ***B*, M-mode color (*top right*) and pulsed-wave Doppler (*bottom right*) analysis in the same patient confirms that turbulent flow below the aortic cusps lasts the whole diastole. AO = aorta; LA = left atrium; LV = left ventricle (reproduced in black and white).**

TABLE I Clinical and Two-Dimensional Echocardiographic Findings in Patients with Systemic Hypertension (SH) and Control Subjects, With and Without Aortic Regurgitation (AR)

	SH with AR (n = 37)	SH without AR (n = 61)	Controls with AR (n = 3)	Controls without AR (n = 24)
SH history length (years)	9.0 ± 7.8	6.7 ± 5.1	—	—
Systolic BP maximum (mm Hg)	203 ± 31	201 ± 24	—	—
Diastolic BP maximum (mm Hg)	110 ± 15	114 ± 15	—	—
Systolic BP study (mm Hg)	165 ± 12	160 ± 11	138 ± 9	136 ± 8
Diastolic BP study (mm Hg)	98 ± 8	96 ± 11	85 ± 6	84 ± 7
Aortic anulus/BSA (cm)	1.7 ± 0.2	1.6 ± 0.3	1.5 ± 0.8	1.5 ± 0.6
Aortic root/BSA (cm)	2.1 ± 0.4	2.0 ± 0.2	2.0 ± 0.3	1.9 ± 0.3
Aortic cusp thickening (%)	92	58*	100	25
Echo LV hypertrophy (%)	54	45	—	—
Echo septal hypertrophy (%)	21	28	—	—

* $p < 0.001$.
BP = blood pressure; BSA = body surface area; LV = left ventricular; SH = systemic hypertension.

mild in 28 and more than mild in 9 patients with SH. AR was mild in all 3 control subjects. AR diastolic murmur was audible in 10 patients with SH and Doppler-defined AR, including all the 9 with more than mild Doppler AR, and in none of the control subjects. Clinical and 2-dimensional echocardiographic findings in patients with SH and control subjects, with and without Doppler AR, are listed in Table I. Thickening of aortic cusps was found in 34 of 37 patients with SH and Doppler AR (92%), 35 of 61 patients with SH and without Doppler AR (58%) and 8 of 27 control subjects (30%) ($p < 0.001$). All 3 control subjects with Doppler AR had aortic cusp thickening.

Our data show that AR can be frequently found by color and pulsed-wave Doppler in patients with long-standing SH, even if an AR murmur is not audible for the mild degree of regurgitation or emphysema. Prevalence of AR by Doppler was greater in our patients with SH than in normotensive control subjects of comparable age range. Confirming previous clinical studies,[1,2] we found that AR is usually mild in patients with SH. Because the assessment of AR by jet length method may be relatively inaccurate,[7] other Doppler methods, such as the estimate of regurgitant orifice width by color Doppler[7] or AR pressure half-time by continuous-wave Doppler,[8] might have provided further information on the real severity of AR in patients with SH. In some patients, continuous-wave Doppler is the only way of recording AR.[8] Then, with a combined use of pulsed- or color and continuous-wave Doppler, a higher prevalence of AR might have resulted in patients with SH than found in our study. We observed that aortic cusp thickening was more common in patients with SH and AR than in those without AR. Moreover, aortic cusp thickening was found in all 3 normotensive control subjects with AR. These data suggest a relation between Doppler AR and morphologic changes of aortic leaflets. Recently, Fisher and Henselman[9] found mild AR, using Doppler, in 7% of a geriatric population with a mean age of 76 years. Fibrosis and calcium deposits on the aortic cusps may be the result of the aging process induced by mechanical wear and tear.[10] We suggest that SH may accelerate this process and determine the occurrence of AR, usually mild and frequently clinically silent, 1 or 2 decades before its appearance in normotensive subjects. In contrast to others,[1,2] we were not able to find in patients with SH any relation between evidence of AR and aortic anulus or root size, duration and severity of SH and presence of left ventricular hypertrophy, concentric or limited to the subaortic portion of ventricular septum.[6] In patients with severe SH, aortic root dilation, by stretching the aortic cusps and hindering their diastolic coaptation, may determine significant AR.[3] This mechanism is probably less important in patients with SH and only mild AR. Transient AR may occur during acute elevation of blood pressure or circulatory overload, particularly in patients with renal failure.[11] Apparently, this mechanism did not influence our findings, because blood pressure was not different at the time of Doppler studies in SH patients with and without AR.

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Early Results of Balloon Angioplasty of Native Aortic Coarctation in Young Adults

IHAB M. ATTIA, MD
ZUHDI A. LABABIDI, MD

Balloon angioplasty of aortic recoarctation has been established as an effective alternative to surgery in young children.[1,2] In spite of several international reports of successful balloon angioplasty of native aortic coarctation,[3-6] there are still controversial opinions regarding its value and long-term results. We report our experience with balloon angioplasty in managing 8 young adults with native aortic coarctation.

From 1983 to 1986, 8 consecutive young adults ranging in age from 19 to 30 years (mean 25 ± 5) with native aortic coarctation underwent balloon angioplasty. One 27-year-old patient has been previously reported.[6] All patients had localized aortic coarctations as confirmed by physical examination, 2-dimensional and Doppler echocardiography. Balloon coarctation angioplasty was performed as described in previous reports.[5,6] The diameter of the balloon was chosen to be equal to or 1 to 2 mm smaller than that of the descending thoracic aorta at the level of the diaphragm. The balloons used ranged in diameter from 15 to 20 mm and were 40 mm long. After confirming the exact location of the balloon by observing its hourglass shape during initial inflation (Figure 1A), the balloon was fully inflated until the hourglass shape disappeared (Figure 1B). In patient 2, follow-up cardiac catheterization was performed 21 months after the angioplasty procedure. The rest of the patients were followed up by physical examination, blood pressure measurement and Doppler echocardiography at an average period of 1 year.

Balloon angioplasty was performed with no significant complications in any of the 8 patients. Minor bleeding at the groin occurred at the time of the procedure. There were no arrhythmias, loss of femoral pulses, cerebrovascular accidents or spinal cord injuries. Table I lists the hemodynamic data obtained for all the patients before and after balloon angioplasty, as well as at follow-up. There was an appreciable decrease in the peak systolic gradient across the coarctation (Figure 2), as well as an increase in the diameter of the coarcted segment in all patients after the procedure (Figure 3). The initial results are promising and the follow-up catheterization performed 21 months later on patient 2 showed a further 8-mm Hg decrease in the gradient. At the 1-year follow-up examination, the residual gradient measured by pulsed-wave Doppler did not exceed 16 mm Hg in any patient. The blood pressure differential between the arms and the legs also did not exceed 15 mm Hg.

Our study showed that early results of balloon angioplasty for coarctation of the aorta in young adults can be as satisfactory as those previously reported in children, provided that meticulous care and appropriate choice of balloon size are undertaken to avoid overdistention of the media of the aortic segments adjacent to the coarctation. The maximum diameter of the balloon should be equal to or 1 to 2 mm less than the diameter of the descending thoracic aorta at the level of the diaphragm, as measured on the video monitor after correction for magnification. The ascending aorta, aortic isthmus and the area just distal to the coarctation are not suitable as a guide for balloon choice because of their marked variability in different patients. Careful manipulation of the guidewire is required at all times after balloon inflation to avoid intimal dissection. The option of balloon angioplasty for adults with

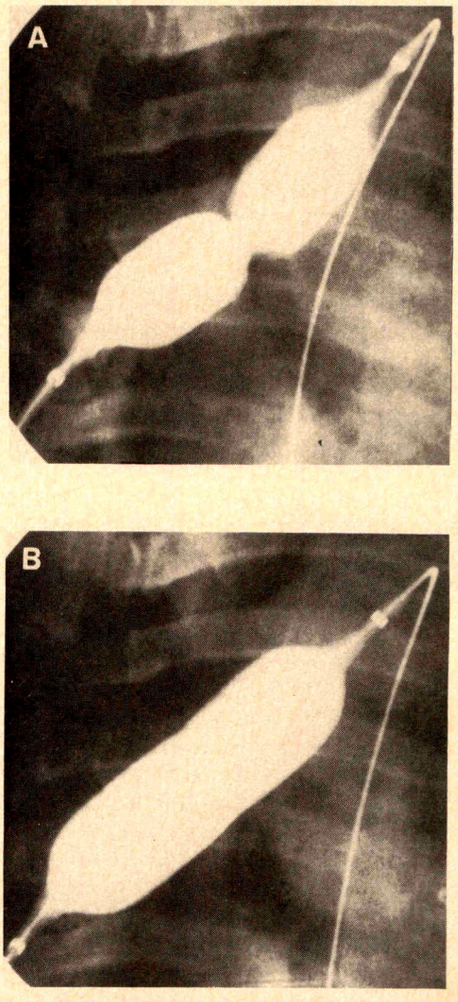

FIGURE 1. ***A*, right anterior oblique view shows the typical hourglass shape of the balloon during initial inflation.** ***B*, the fully inflated balloon demonstrates disappearance of the hourglass shape, indicating satisfactory dilatation.**

From the Division of Pediatric Cardiology, University of Missouri-Columbia Hospital and Clinics, Columbia, Missouri.
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TABLE I Hemodynamic Results of Balloon Angioplasty for Native Aortic Coarctation in Young Adults

Pt	Age (yrs)	Before BA PSG (mm Hg)	After BA PSG (mm Hg)	Diameter Before BA Co (mm)	Diameter After BA Co (mm)	Balloon Diameter (mm)
1	27	70	15	6	12	18
2	19	65	13	6	14	15
3	20	33	5	11	15	20
4	20	22	5	7	26	20
5	30	63	7	4	12	18
6	28	23	3	9	18	20
7	22	50	0	6	13	18
8	31	55	12	6	10	18
Mean	25	48	7	7	15	18
±SD	±5	±19	±5	±2	±5	±2

BA = balloon angioplasty; Co = coarctation; PSG = peak systolic gradient; SD = standard deviation.

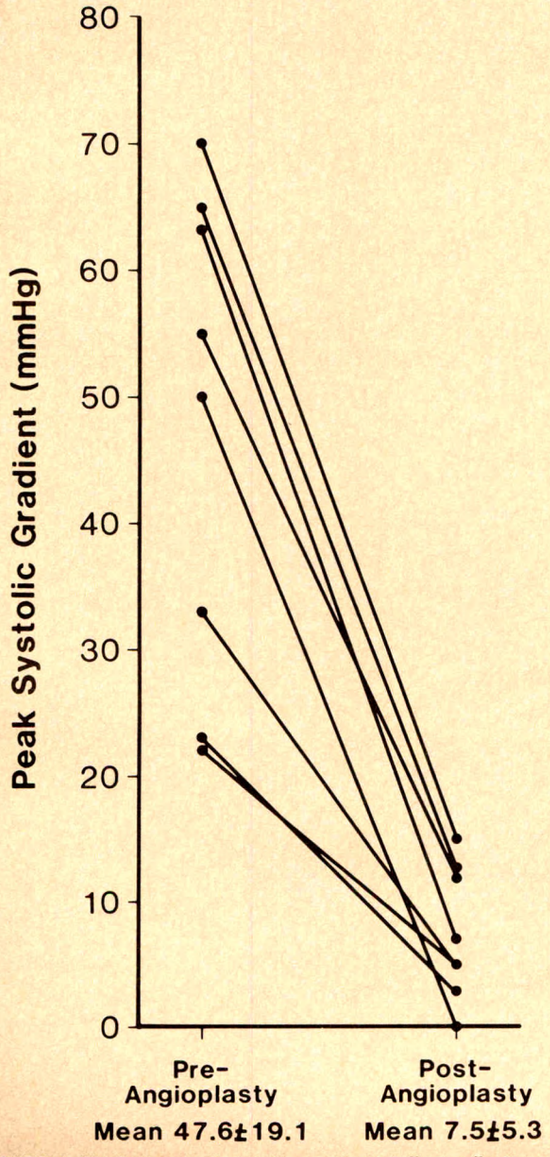

FIGURE 2. Marked reduction in the peak systolic gradient across the coarctation immediately after balloon coarctation angioplasty.

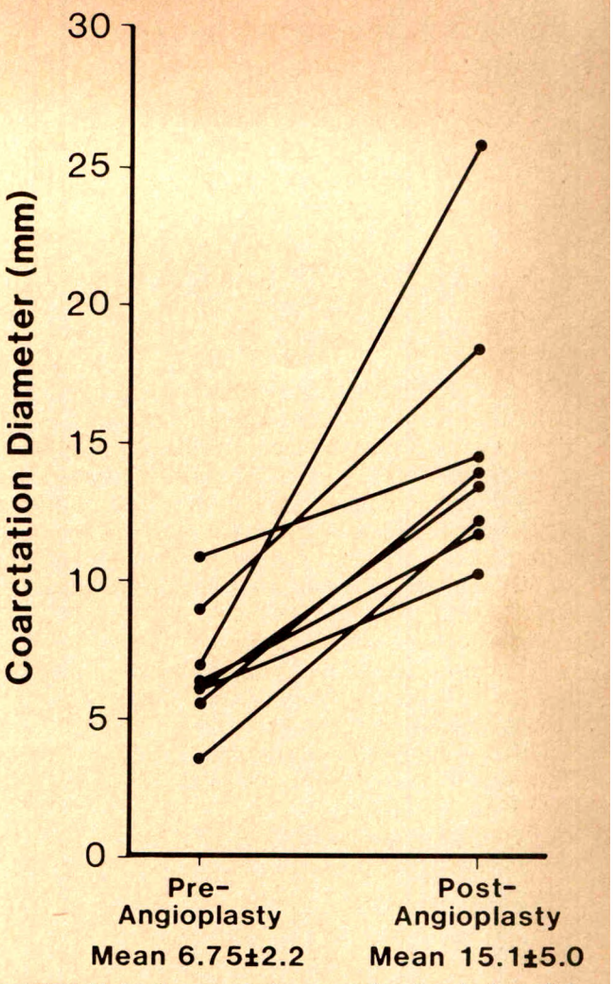

FIGURE 3. Marked increase in the coarctation diameter immediately after balloon coarctation angioplasty.

native aortic coarctation is worthy of consideration and provides the established advantages of balloon angioplasty over surgery. The frequent occurrence of an aneurysm at the site of surgical coarctation repair, several years after the various types of surgical repair of coarctation of the aorta, poses a challenge to the future long-term results of balloon angioplasty for native aortic coarctation. Thus, further studies involving adults with native aortic coarctation should be undertaken. Our initial experience is encouraging and long-term follow-up studies are required.

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Effects of Repeated Increments in Right Atrial Pressure on Secretion of Atrial Natriuretic Factor

MATHIAS C. HAUFE, MD
JOCHEN WEIL, MD
RUPERT GERZER, MD
JOHANNA E. ERNST
KARL THEISEN, MD

It has been demonstrated that an acute increase in right atrial (RA) pressure and paroxysmal supraventricular tachycardias induce the release of atrial natriuretic factor (ANF).[1-4] In a previous study that allowed a selective or combined increase in heart rate and RA pressure by intracardiac pacing, we showed that acute increment in RA pressure is the determinant factor for ANF secretion.[5] Hollister et al[3] demonstrated that, in subjects with elevated ANF levels due to a high salt diet, ANF release caused by atrial pressure increment was higher compared with subjects with normal baseline ANF. These data suggest that under chronically stimulated ANF secretion, there might be a higher sensitivity of ANF release to additional secretory stimuli. However, it is unknown whether there is an adaptation of the ANF release to repetitive secretion stimuli. We therefore investigated the ANF response to repeated identical atrial pressure increments.

Eight patients (7 men, 1 woman, ages 38 to 63 years) with moderate coronary artery disease were studied before a diagnostic right- and left-sided heart catheterization. All patients had normal ventricular and atrial pressures, a left ventricular ejection fraction >40% and stable sinus rhythm at rest. Nitrates, β blockers and calcium antagonists were terminated at least 48 hours before the examination. None of the patients was taking digitalis. All patients had given their informed consent.

As previously reported,[5] right ventricular pacing in patients with sinus rhythm results in an asynchronous contraction of the right ventricle and atrium and leads to an acute increment in RA pressure and subsequently to ANF release.

All patients underwent right ventricular pacing at 150 beats/min for a period of 4 minutes (stimulation I). After a 15-minute interval, the identical stimulation was repeated (stimulation II). RA pressure and systemic blood pressure were continuously measured through catheters placed in the right atrium and the femoral artery. A bipolar lead and a programmable external pacemaker were used for stimulation. The electrocardiogram was monitored throughout the whole study.

Arterial blood samples were taken in ice-water-cooled Ethylene-diaminotetraacetate tubes before and after stimulation I and stimulation II, and immediately separated by centrifugation at 2°C and 2,800 rounds/min and stored at −70°C until assayed. Plasma ANF concentration was measured after extraction through octadecyl-silane cartridges (Sep-pak C18). The absorbed ANF was eluted with 86% ethanol in 4% acetic acid. After evaporation and lyophilization the dry residue was dissolved in radioimmunoassay

From the Medizinische Klinik Innenstadt, University of Munich, Ziemssenstrasse 1, 8000 Munich 2, Federal Republic of Germany. Manuscript received July 31, 1987; revised manuscript received and accepted November 24, 1987.

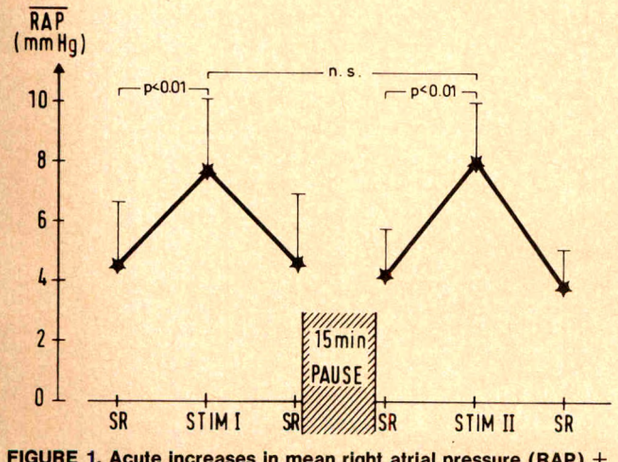

FIGURE 1. Acute increases in mean right atrial pressure (RAP) ± standard deviation by right ventricular stimulation I and II (Stim I, Stim II, both at 150 beats/min). NS = not significant; SR = sinus rhythm.

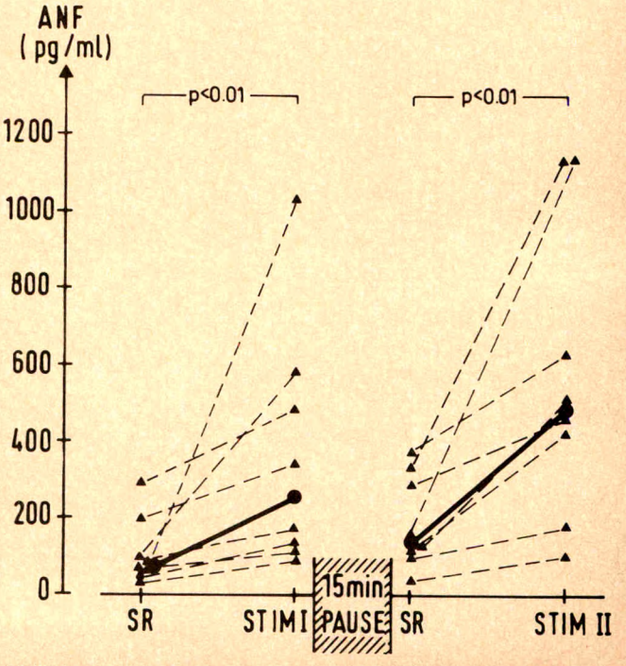

FIGURE 2. Atrial natriuretic factor (ANF) plasma concentrations during stimulations I and II (Stim I, Stim II) for each patient. *Dots* are median values. SR = sinus rhythm before both stimulations.

buffer for determination of ANF using an incubation time of 48 hours at 4°C. Separation of free from antibody-bound iodine-125-α-ANF was achieved by a double-antibody method. The inter- and intraassay variation was 15% and 11%, respectively. In 86 control subjects (ages 20 to 45 years), the plasma ANF levels ranged from 30 to 125 pg/ml (median 74).

Plasma levels of cyclic guanosine monophosphate were measured by radioimmunoassay of ethanol extracted samples.[2]

For statistical analysis the Wilcoxon test was used. P values <0.05 were considered significant.

Figure 1 illustrates the increment in mean RA pressure. Mean RA pressure increased from 4.5 ± 2.3 mm Hg at control (sinus rhythm) to 7.7 ± 2.5 mm Hg ($p < 0.01$) during stimulation I and dropped immediately after termination of stimulation I to control values. Stimulation II increased mean RA pressure comparably from 4.2 ± 1.7 to 7.9 ± 2.2 mm Hg ($p < 0.01$). Control values at sinus rhythm before and the amount of RA pressure increments during both stimulations did not differ (difference not significant). Mean systemic blood pressure remained stable throughout the whole protocol.

Figure 2 shows ANF levels during stimulation I and II. The median of control values before stimulation I was 79 pg/ml (range 46 to 299) and increased significantly ($p < 0.01$) to 258 pg/ml (range 96 to 1,045). At the end of the 15-minute interval, ANF values had decreased almost to control values (difference not significant). Median ANF before stimulation II was 140 pg/ml (range 42 to 375) and was significantly ($p < 0.01$) increased by stimulation II up to 488 pg/ml (range 107 to 1,145).

The statistically different ANF secretion in both stimulations is shown in Figure 3. Median ANF increase during stimulation I was 116 pg/ml (range 44 to 974) compared with 290 pg/ml (range 65 to 989) during stimulation II; i.e., the amount of ANF released by stimulation II was 2.5-fold higher than by stimulation I ($p < 0.02$).

Median cyclic guanosine monophosphate levels (Figure 4) showed a similar trend and increased from 3.1 to 4.9 pmol/ml after stimulation I and from 5.4 to 8.5 pmol/ml after stimulation II. There was a significant and linear correlation between control cyclic guanosine monophosphate and ANF levels ($r = 0.79$, $p < 0.05$).

Our results indicate, for the first time, that repeated stimulation of the ANF secretory system enhances ANF release. The myoendocrine cells are apparently capable of a fast upward regulation of their response to adequate secretory stimuli.

RA pressure modulates the ANF secretion. Diseases as well as maneuvers, which induce RA pressure increment, lead to enhanced ANF levels.[2-6] As previously shown, rapid ventricular pacing in patients with sinus rhythm provokes immediate and reproducible increases in RA pressure and ANF release.[5]

Up to now, no studies have investigated the ANF response to repeated secretory stimuli. From other hormone systems it is known that there is no uniform response. Insulin, for example, shows an enhanced release[7] after repeated stimulation. In the present study, while RA pressure was identically increased in both stimulations, the amount of ANF secretion after the second stimulation was significantly larger than the ANF release that followed the first stimulation. As expected from the known half-time of ANF, ANF levels had markedly dropped in the 15-minute interval before the second stimulation. There was no statistically significant difference between ANF levels before the first and the second stimulation.

The correlation between baseline cyclic guanosine monophosphate and ANF levels that we found in this

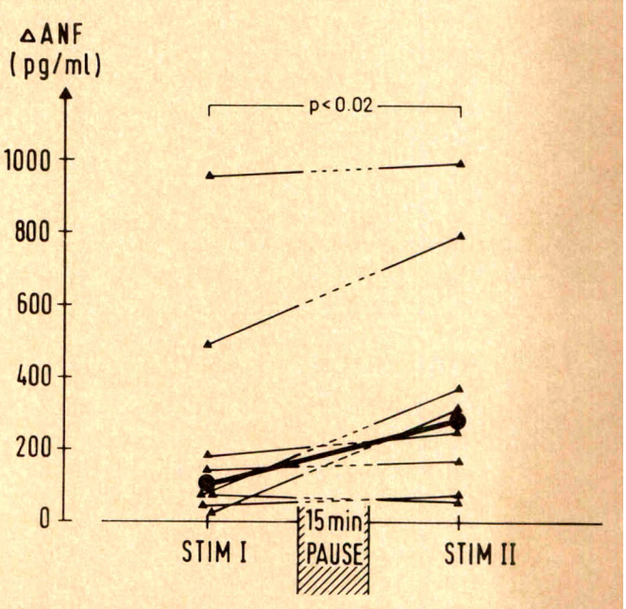

FIGURE 3. Increases (Δ values) in atrial natriuretic factor (ANF) plasma concentrations during stimulations I and II (Stim I, Stim II) for each patient. *Dots* are median values. SR = sinus rhythm before both stimulations.

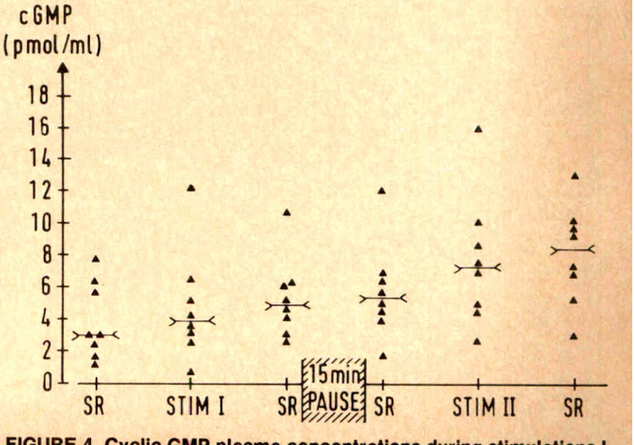

FIGURE 4. Cyclic GMP plasma concentrations during stimulations I and II (Stim I, Stim II). *Horizontal lines* are median values. SR = sinus rhythm before both stimulations.

study is comparable to data recently reported.[8] Increases in median cyclic guanosine monophosphate levels were 1.8 pmol/ml after the first stimulation and 3.1 pmol/ml after the second stimulation and corresponded to the higher release of ANF after the second stimulation. Between both stimulations, cyclic guanosine monophosphate had not decreased, which can be explained by a time difference between peaks of ANF and cyclic guanosine monophosphate, and a markedly longer half-time of cyclic guanosine monophosphate of about 30 minutes, as demonstrated in a previous study.[9]

According to our results, the first secretory stimulus, RA pressure increment, appears to have a "priming effect" on the ANF release caused by an identical second stimulus. According to published reports, a correlation between ANF concentrations and its biologic effects can be anticipated.[9]

In addition, the increase in cyclic guanosine monophosphate, known as the second messenger of ANF,[10] confirmed the primed ANF secretion measured after the second stimulation.

The myoendocrine cells appear to be quickly adaptable to a higher secretion. Possible underlying mechanisms, i.e., propagation of granular exocytosis, enhanced intracellular conversion from progranules to granules or increased ANF reduplication, have to be resolved in further studies.

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Lipoprotein Profiles of Elite Veteran Endurance Athletes

ROBIN J. NORTHCOTE, MD
GORDON C. CANNING, MRCP
IAIN C. TODD, BSc, MRCP
DAVID BALLANTYNE, MD

The long-term effect of exercise training on plasma lipoproteins has not been described, although the short-term effects of exercise have shown an improvement in the lipoprotein profile with regard to coronary artery disease (CAD) risk.[1] We report our findings in a group of veteran endurance runners.

Three groups of subjects were studied. Group 1 consisted of 20 male endurance runners recruited from the Scottish Veteran Harriers Club. These men were recruited on the basis of a minimum age of 45 years, minimum running experience of 15 years and minimum weekly training of 30 miles. All athletes had not run for at least 2 days before study. Group 2 consisted of 20 men who undertook light physical activity in the form of golf, bowls or walking. All subjects in groups 1 and 2 were healthy with no history of cardiovascular disease, cigarette smoking, heavy alcohol consumption, renal or hepatic disease or diabetes mellitus and none was on a special diet or took dietary supplements, stimulants or other medication. Group 3 consisted of 20 matched male patients recruited from a cardiac clinic with symptomatic CAD (New York Heart Association grade II to III) confirmed by selective coronary angiography (n = 12) or exercise electrocardiography (n = 8). No subject was taking medication at the time of study, apart from sublingual triceryl trinitrate for episodes of chest pain. Eight of

TABLE I Characteristics of the Three Study Groups

	Endurance Athletes (n = 20)	Control Subjects (n = 20)	CAD Patients (n = 20)
Age (yrs)	56 ± 7	56 ± 7	54 ± 10
Running experience (yrs)	36 ± 7 (28–50)	—	—
Miles/week	47 ± 23 (25–110)	—	—
Best marathon time (min)	175 ± 23 (2.25–3.40)	—	—
Resting HR (beats/min)	51 ± 7	72 ± 10*	68 ± 9*
Systolic BP (mm Hg)	125 ± 15	135 ± 23*	128 ± 18
Max treadmill exercise time (Bruce protocol) (min)	19 ± 4	16 ± 2	—
Height (m)	1.75 ± 0.048	1.74 ± 0.079	1.75 ± 0.07
Weight (kg)	64 ± 5	74 ± 8	75 ± 10
Quetelet index ($kg/cm^2 \times 10^3$)	2.24 ± 0.01	2.45 ± 0.25	2.45 ± 0.30
Body fat (%)	9 ± 3	15 ± 4*	—

* $p < 0.01$.
BP = blood pressure; CAD = coronary artery disease; HR = heart rate.

From the Department of Medical Cardiology, Victoria Infirmary, Glasgow G42 9TY Scotland. Manuscript received June 22, 1987; revised manuscript received November 16, 1987, and accepted November 22.

Dr. Canning's present address: Department of Geriatric Medicine, Southern General Hospital, Glasgow.

TABLE II Lipoprotein Plasma Analyses

	Endurance Athletes (n = 20)	Control Subjects (n = 20)	CAD Patients (n = 20)
Total cholesterol	242 ± 31	233 ± 32	274 ± 55*
VLDL	19 ± 10	30 ± 25†	32 ± 15†
LDL	164 ± 29	158 ± 29	192 ± 50†
HDL	58 ± 11	45 ± 11†	49 ± 7*
HDL_2	67 ± 25	49 ± 29‡	27 ± 16‡
HDL_3	232 ± 57	195 ± 43†	224 ± 43
HDL_2/HDL_3	0.30 ± 0.13	0.25 ± 0.14†	0.12 ± 0.08‡
HDL/total cholesterol	0.24 ± 0.05	0.19 ± 0.04†	0.19 ± 0.06†
Total triglyceride	103 ± 37	147 ± 91†	172 ± 58‡

* $p < 0.05$; † $p < 0.01$; ‡ $p < 0.00$.
CAD = coronary artery disease; HDL = high density lipoprotein; LDL = low density lipoprotein; VLDL = very low density lipoprotein.

these men were previously known to have had a myocardial infarction at least 1 year before this study. Percentage of body fat was calculated by incorporating tricepts, scapular and abdominal skin-fold thickness into the equation devised by Lohman.[2]

Blood was withdrawn from all subjects in the sitting position after an overnight fast (14 to 16 hours). No vigorous exercise was performed in the previous 48 hours.

Lipoprotein subfractions were separated using the technique of preparative ultracentrifugation and heparin/magnesium chloride precipitation followed by lipid analysis of the resultant fractions. The cholesterol and triglyceride concentration in the fractions A (very low density lipoprotein [VLDL]), B (low density lipoprotein [LDL]) and C (high density lipoprotein [HDL]) were measured. The concentration of LDL was obtained by subtracting the HDL cholesterol concentration from that in fraction B. Plasma total triglycerides were estimated by a fully enzymatic method on a Technicon auto-analyzer (second generation). Plasma total cholesterol was estimated by an enzymatic colorimetric method using a modified Lieberman-Burchard reaction. HDL was further subfractioned into the components HDL and HDL_3 by rate zonal ultracentrifugation. Lipoprotein subfractions are expressed in mg/dl followed by mmol/liter.

Results are expressed as mean ± standard deviation. Both Student's paired t test and Wilcoxon's signed rank test were applied to the lipoprotein results. The most conservative estimates of significance are reported.

The 3 groups were closely matched in terms of age (Table I). Predictably, both resting heart rate, body mass (Quetelet index) and percentage of body fat were lower in the athletic group. Group 1 consisted of an elite group of veteran runners with excellent performances in marathons (Table I) of national and international scope.

The results of the lipoprotein analyses are listed in Table II. Total triglyceride was significantly higher in both control subjects and those patients with CAD, but total cholesterol was higher in both athletes (difference not significant) and CAD patients ($p < 0.05$) compared with control subjects. VLDL cholesterol was significantly higher in both control subjects (group 2) and those patients with CAD (group 3) but LDL was only higher in CAD patients ($p < 0.01$); the level in the athletes was higher than those found in healthy control subjects (difference not significant). Both total HDL and HDL_2 were significantly lower in control subjects and those patients with CAD ($p < 0.001$). The ratios of HDL_2 to HDL_3 and HDL to total cholesterol were significantly higher in the athletes.

The veteran endurance athletes in this study had a remarkably higher HDL_2 level: 37% higher than their lean sedentary peers. This indicates an approximately 2.5-fold increased greater risk for the latter group compared with athletes of developing CAD according to Framingham data,[3] independent of other risk factors. The athletes had levels 250% higher than those patients with proven CAD. The groups involved in the study were closely matched in physical terms but it could be argued tht the difference in lipoproteins reflected differences in body composition. The athletes had a significantly lower percentage of body fat than their sedentary peers but no significant relation was found between HDL_2 levels and percentage of body fat. Thus the higher HDL and HDL_2 concentrations appear to be a direct result of lifelong running rather than body composition. Previously, differences in HDL concentrations between trained and sedentary individuals have not been related to differences in diet. In this study, no participant was on a special or unusual diet. Thus, although dietary analyses were not part of the study it is unlikely that any difference in dietary habit substantially altered the results.

Previous studies have reported significantly higher total HDL cholesterol levels in individuals taking part in an exercise training program,[1,4–7] but none has measured the HDL subfractions. It is probable that the acute effect of exercise training on the lipoprotein profile reported by others[6] is sustained and results in a substantial reduction in CAD risk if continued throughout life. The mechanism whereby exercise increased total HDL and HDL_2 is not known; however, Kantor et al[8] demonstrated a substantial increase in post-heparin plasma lipoprotein lipase activity in marathon runners for up to 2 days following a 42-km race.

This may explain the increase in total HDL and reduction in triglycerides that they demonstrated, and would be consistent with our results.

Acknowledgment: We wish to especially thank the members of the Scottish Veteran Harriers Club for their cooperation with this study. We also wish to acknowledge the technical assistance of Dorothy Bedford of the University Department of Pathological Biochemistry, the Royal Infirmary, Glasgow, and Margaret Stewart for secretarial help.

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Idioventricular Rates in Early and Late Phases of Acute Myocardial Infarction

JAOK HAN, MD, PhD
MYUNG S. YOON, MD
GEORGE H. DERSHAM, PhD

Two distinct phases of ventricular arrhythmias are observed after coronary artery occlusion in the dog.[1] An early arrhythmic phase begins almost immediately and persists up to a few hours; then, a late phase begins at 12 to 24 hours and lasts approximately 24 hours. Experimental data seem to indicate that the early arrhythmias result from reentry associated with abnormal conduction in the ischemic myocardium, whereas the late arrhythmias are due to enhanced automaticity of Purkinje fibers.[2,3] The present study compares the degrees of ventricular automaticity during the early and late phases of acute myocardial infarction in dogs with complete atrioventricular (AV) block and idioventricular escape rhythm.

From the Department of Medicine (Cardiology), Albany Medical College of Union University, and the Electrocardiography Laboratory, Albany Medical Center Hospital, Albany, New York. This study was supported by a grant from the American Heart Association (New York State Affiliate), and by the Cardiology Research Fund of Albany Medical College, Albany, New York. Manuscript received September 8, 1987; revised manuscript received December 7, 1987, and accepted December 8.

Experiments were performed on 10 mongrel dogs anesthetized by an intravenous injection of sodium pentobarbital (30 mg/kg). The dogs were ventilated by artificial respiration through an endotracheal tube. A bipolar electrode catheter was introduced into the right femoral vein and advanced to the region of His bundle. The His bundle electrogram was recorded along with lead II electrocardiogram on an Electronics for Medicine recorder at a paper speed of 100 mm/s. After the stable His electrogram was secured, ablation of the His bundle was attempted by way of the His bundle electrode catheter. The cathodal output of a standard defibrillator unit was connected to the distal pole of the His electrode catheter and the anodal output was connected to the paddle placed over the left precadium. A high-energy discharge of 200 to 300 joules was delivered to the His bundle electrode to obtain the stable AV block which resulted in idioventricular escape rhythm. This was repeated in some dogs to secure long-standing complete AV block. Figure 1 illustrates lead II electrocardiograms and His bundle electrograms recorded before and after the successful His bundle ablation. After the stable idioventricular escape rhythm was established, the chest was opened by left thoracotomy and the pericardium was opened to expose the proximal and mid portions of the left anterior descending artery for later ligation. The idioventricular rate was determined as a measure of baseline ventricular automaticity. The left anterior

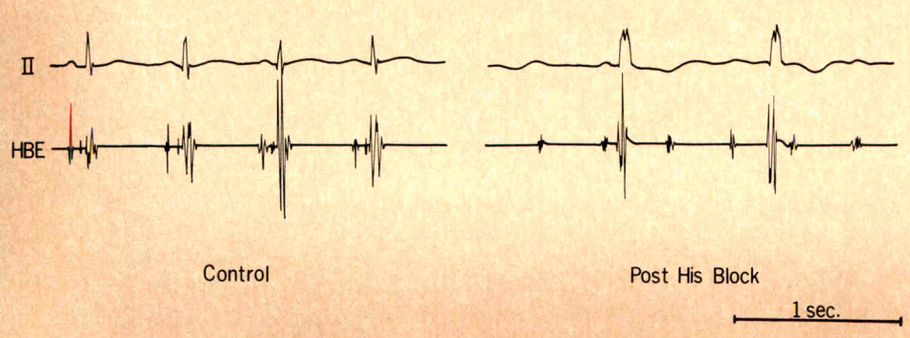

FIGURE 1. Lead II electrocardiograms and His bundle electrograms before (control) and after the His bundle ablation (block). HBE = His bundle electrogram.

descending artery was then occluded above the diagonal branch by the Harris 2-stage ligation technique.[1] The idioventricular rate was again determined at 15 to 45 minutes after coronary occlusion. The pericardium and the thorax were subsequently closed and an airtight seal maintained while the dogs were allowed to recover from the anesthesia. After 24 hours the dogs were reanesthetized, their chests were reopened and ventricular automaticity was again assessed using the same methods as those used on the previous day.

Figure 2 shows the mean idoventricular rates in the control state, at 15 to 45 minutes and at 24 hours after coronary occlusion. The mean rates were 86 ± 7/min in the control state and 85 ± 7/min at 15 to 45 minutes after coronary occlusion. The difference was not statistically significant. The mean rate was increased to 171 ± 9/min at 24 hours after coronary occlusion and this increase was statistically significant ($p < 0.001$) compared with the mean rate during the control state or at 15 to 45 minutes after coronary occlusion. The increased idioventricular rate at 24 hours after coronary occlusion was predominantly due to acceleration of the rhythm of the same QRS morphology in 5 of the 10 dogs. An example of such a rate increase in the same QRS pattern is shown in Figure 3. In the remaining 5 dogs, the QRS morphology at 24 hours after coronary occlusion was different from that of either the control state or at 15 to 45 minutes after coronary occlusion. As depicted in Figure 4, the QRS patterns were often multiform.

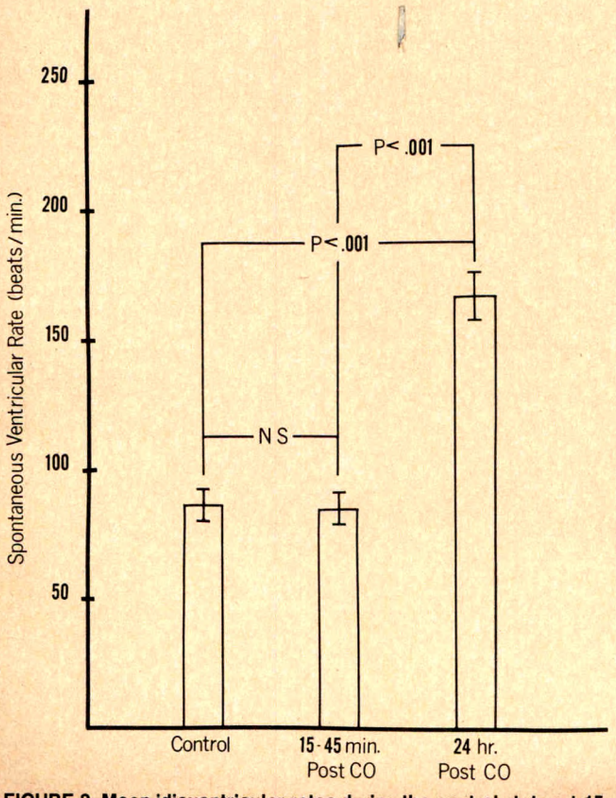

FIGURE 2. Mean idioventricular rates during the control state, at 15 to 45 minutes and at 24 hours after coronary occlusion (CO). NS = not significant.

Our present knowledge of the electrophysiologic mechanisms of ventricular arrhythmias has been largely obtained from canine experiments. It has been generally accepted that the early arrhythmias result from reentry and the late ones are due to enhanced automaticity.[2,3] The early arrhythmic phase in the dog could be related to the prehospital phase of arrhythmias seen during acute myocardial infarction in humans, while the late arrhythmic phase may be similar to the in-hospital arrhythmias. In the present study, the idioventricular rates were assessed in the early and late phases of acute myocardial infarction using the same dogs and with each dog serving as its own control. The results showed that the mean idioventricular rate does not change significantly during the early

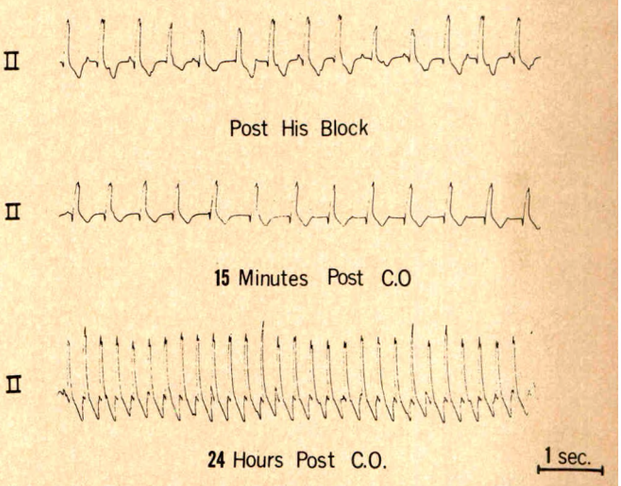

FIGURE 3. Lead II electrocardiograms from 1 of the experiments after the His block before coronary occlusion, at 15 minutes and at 24 hours after coronary occlusion (C.O.).

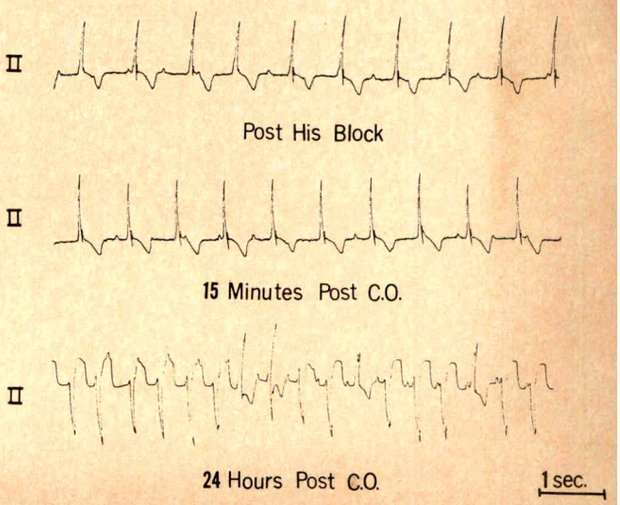

FIGURE 4. Lead II electrocardiograms from another experiment shows multiform QRS patterns.

phase of acute myocardial infarction but is significantly increased during the late phase. These observations are in agreement with earlier dog experiments in which the ventricular Purkinje fibers remained intact for approximately 10 to 12 hours and the structural changes began to appear at 12 to 24 hours after coronary occlusion.[3,4] The damaged Purkinje fibers showed abnormal electric activity, such as reduced resting membrane potential and spontaneous diastolic depolarization.[4,5] These spontaneously depolarizing Purkinje fibers may result in increased automaticity and ventricular arrhythmias. Indeed, the present study indicates that enhanced automaticity is of little importance in the genesis of early ventricular arrhythmias but may play a significant role in the development of late arrhythmias during acute myocardial infarction. Other possible mechanisms for the late arrhythmias are reentry and triggered activity arising from damaged Purkinje tissues.[3]

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The AJC in April 1963

WILLIAM C. ROBERTS, MD

The AJC in April 1963 contained 20 articles, occupying 133 pages, and they included 8 major studies, 2 experimental studies, 1 historic study and 9 case reports. Five of the 8 major studies and 8 of the 9 case reports concerned patients with congenital heart disease. This piece will comment on 4 of the 20 articles.

Moncada and associates[1] from Chicago, Illinois, described left ventricular angiographic findings in 35 infants and children with ventricular septal defect (VSD). The angiograms demonstrated shunting of the contrast material into the right ventricle in all 35 patients. The defect was "membraneous" in 21, "high muscular" in 9 and "low muscular" in 4. The authors concluded that left ventricular angiography was useful in indicating the presence, location, size and number of VSDs, and the existence of associated intracardiac anomalies of the left side of the heart.

Karnegis and Wang[2] from Minneapolis, Minnesota, measured the interval between the onset of the Q wave on the electrocardiogram and the first heart sound on the phonocardiogram (Q-1 interval) in 13 patients with VSD and found the interval to be relatively proportional to the size of the shunt through the VSD—the larger the shunt, the longer the interval.

Elliott and associates[3] from Minneapolis, Minnesota, described clinical and necropsy findings in 3 patients with single ventricle, normally related ascending aorta and pulmonary trunk, and obstruction to pulmonary flow. Most patients with single ventricle have transposed great arteries and no obstruction to pulmonary flow.

Samet and associates[4] from Miami Beach, Florida, illustrated indicator dilution curves following injections of indocyanine green in complicated atrial septal defect (Ebstein's anomaly of the tricuspid valve, total anomalous pulmonary venous connection, tricuspid valve atresia and anomalously connected left pulmonary vein).

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Coronary Artery Spasm, Cardiac Arrest, Transient Electrocardiographic Q Waves and Stunned Myocardium in Cocaine-Associated Acute Myocardial Infarction

ELIZABETH K. ASCHER, MD
JEAN-CHRISTOPHE E. STAUFFER, MD
WILLIAM H. GAASCH, MD

Recreational cocaine use has recently been recognized as a cause of acute myocardial infarction (AMI), even in patients with normal coronary arteries.[1-11] The pharmacologic effects of this drug are sympathomimetic; they include peripheral potentiation of catecholamine activity, inhibition of monoamine oxidase activity and direct central medullary stimulation. In previous reports relating nasal or intravenous cocaine use to AMI, angiography has frequently shown little or no fixed obstructive coronary artery disease.[2-5,8,10,11] Although ergonovine testing has been negative in reported cases,[4,5,8,10,11] cocaine-induced coronary artery spasm has been presumed to be responsible for AMI in these patients. We describe a cocaine user who had an AMI, in whom unprovoked coronary artery spasm was documented.

A 47-year-old white man was admitted to the hospital with severe chest pain beginning 15 hours after the intake of undetermined quantities of cocaine (intranasal), alcohol (oral) and marijuana (inhaled). He was a longstanding cigarette smoker, but had no known history of cardiovascular disease, diabetes mellitus or hyperlipidemia. The admission electrocardiogram showed significant Q waves and 3-mm ST elevation in leads V_2 through V_4 (Figure 1A). Within 30 minutes of admission, the patient developed ventricular fibrillation and immediately underwent successful cardioversion. Shortly thereafter, the chest pain resolved, and a repeat electrocardiogram revealed only ST-segment depression in V_4; the Q waves were no longer present (Figure 1B). Serum creatine kinase levels peaked at 1,053 (IU/liter) with a 15% MB-isoenzyme fraction 18 hours after admission. On the day after admission, an echocardiogram showed extensive left ventricular wall motion abnormality (anteroseptal and apical akinesis). The left ventricular ejection fraction by radionuclide ventriculogram was 29%. Initial treatment with metoprolol (25 mg orally 2 times daily) and aspirin (325 mg orally once daily) was begun.

Five days after admission, left ventriculography showed anterior, apical and inferior wall akinesis

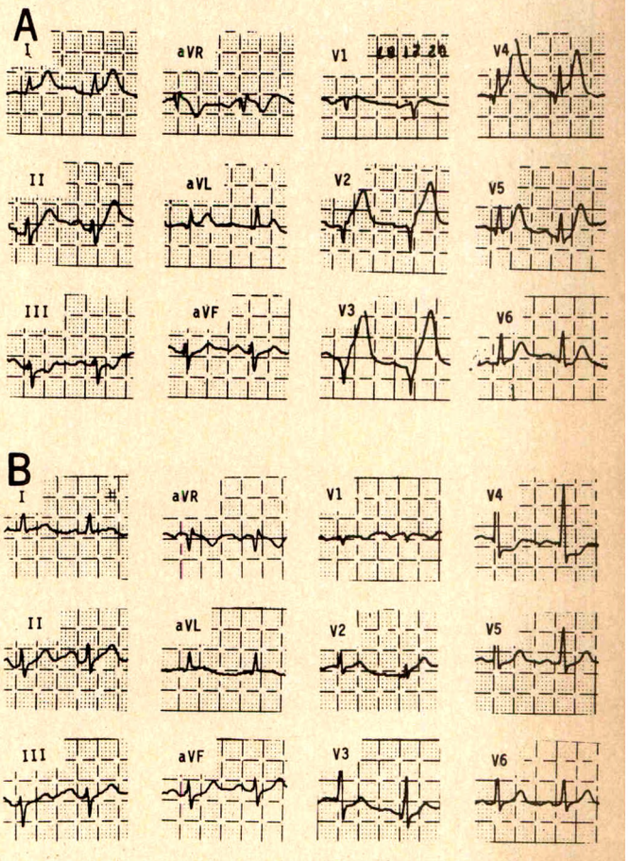

FIGURE 1. Electrocardiogram from a patient with cocaine-associated myocardial infarction. In *A*, the electrocardiogram shows Q waves and ST elevation in leads V_2 through V_4 consistent with acute myocardial infarction. In *B*, taken after cardioversion, the electrocardiogram shows resolution of the infarct pattern; ST-segment depression persists and later showed evolution consistent with a non-Q-wave myocardial infarction.

From the Department of Medicine (Cardiology), Tufts University School of Medicine, and the Boston Veterans Administration Medical Center, Boston, Massachusetts. Manuscript received October 6, 1987; revised manuscript received and accepted December 12, 1987.

with an ejection fraction of 45%. Selective coronary arteriography revealed <20% diameter narrowing of the mid-left anterior descending coronary artery. Spontaneous spasm at this site resulted in diameter narrowing of the lumen by 80% (Figure 2A). This dynamic narrowing resolved after administration of sublingual nitroglycerin (0.4 mg) (Figure 2B). Metoprolol was discontinued, and the patient was treated with diltiazem (30 mg orally 4 times daily); he remained asymptomatic thereafter.

On exercise testing before discharge, the patient had no clinical or electrocardiographic evidence of myocardial ischemia at a heart rate of 98 beats/min during stage 4 of the Naughton protocol. A radionuclide ventriculogram 1 month after discharge showed normal left ventricular wall motion; the systolic ejection fraction was 59%. A second echocardiogram 2 months after discharge showed normalization of the previously observed wall motion abnormality; the global ejection fraction appeared normal.

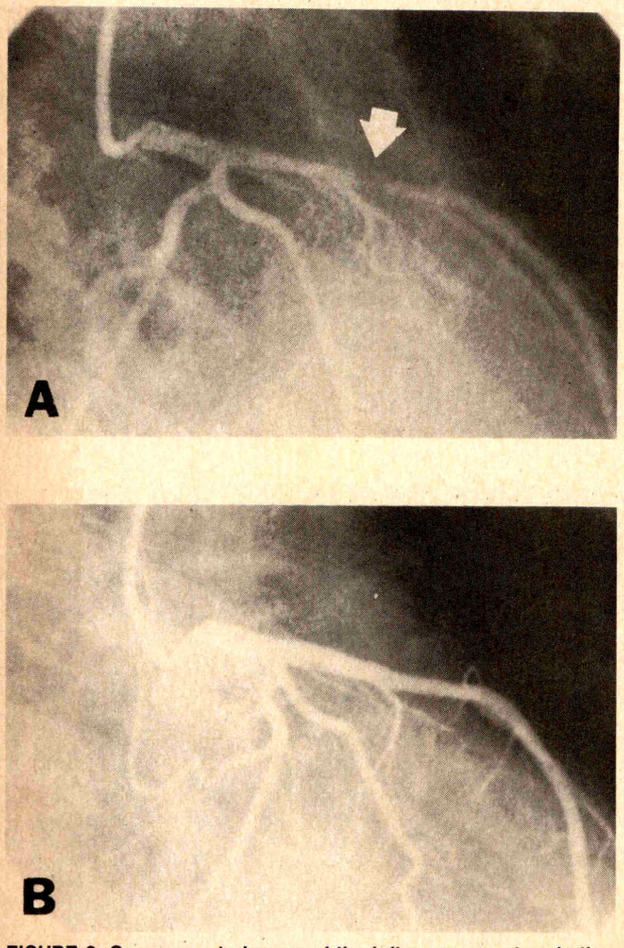

FIGURE 2. Coronary arteriogram of the left coronary artery in the right anterior oblique projection. In *A*, there is a near-total occlusion (spasm) of the proximal left anterior descending coronary artery (*arrow*). In *B*, the left anterior descending artery (filmed after nitroglycerin administration) appears nearly normal.

Cocaine-induced increases in the left ventricular pressure-rate product and myocardial oxygen demand represent a predictable risk for patients with underlying coronary artery disease. In patients with normal coronary arteries, mechanisms that can explain AMI include coronary artery spasm or in situ thrombosis. Our case is the first report of AMI with cocaine use in which coronary spasm of the infarct-related artery was documented by angiography; this extends the likelihood that cocaine-induced coronary spasm was the cause of AMI.

In concurrence with 38 previous case reports of AMI associated with cocaine use, our patient was relatively young and had no risk factors for coronary artery disease aside from cigarette smoking.[1-11] More important, he had no previous symptoms to suggest an underlying vasospastic syndrome such as Prinzmetal's variant angina, nor was he using ergonovine or drugs known to produce or exacerbate spasm.

Evidence that focal coronary spasm was the inciting event in this patient's illness is provided by his clinical course. On admission, the electrocardiogram suggested severe transmural ischemia; abruptly, he developed ventricular fibrillation, followed by resolution of chest pain and the near-normalization of electrocardiographic abnormalities. This sequence is consistent with reperfusion of ischemic myocardium after relief of dynamic coronary obstruction. Transient abnormal Q waves, as seen in this case, have been described during episodes of ischemia in both classic angina and Prinzmetal's variant angina. The mechanism of this phenomenon is felt to be reversible loss of electrical activity due to localized alterations in the cell membranes in severely ischemic but still viable tissue.[12]

Coronary vasospasm, in the presence or absence of coronary atherosclerosis, can cause a wide spectrum of clinical syndromes ranging from transient myocardial ischemia to irreversible infarction with permanent ventricular dysfunction. In between these 2 extremes, our patient manifested reversible postischemic left ventricular dysfunction, with enzymatic evidence of myocardial necrosis. Heart muscle that exhibits prolonged but reversible contractile dysfunction after coronary occlusion has been termed "stunned."[13] Although originally described as dysfunction that persists without evidence of necrosis, "stunning" apparently may also occur, as in our patient, in the surviving myocardium adjacent to, or within, a necrotic area after infarction.[14] As illustrated by this case, the presence of severe left ventricular dysfunction early after AMI may not be permanent.

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Sudden Death in Hemochromatosis After Closed-Chest Catheter Ablation of the Atrioventricular Junction

ROBERT LEMERY, MD
PEDRO BRUGADA, MD
MICHAEL HAVENITH, MD
DEBORAH BARBOUR, MD
WILLIAM C. ROBERTS, MD
HEIN J.J. WELLENS, MD

In patients with supraventricular tachycardia refractory to antiarrhythmic drugs or antitachycardia pacemakers, closed-chest catheter ablation of the atrioventricular (AV) junction is an alternative to surgery.[1,2] We report clinical and necropsy findings in a patient who died suddenly 1 week after catheter ablation of the AV junction.

A 47-year-old man with hemochromatosis since age 25 had evidence of congestive heart failure since age 44 and paroxysmal atrial fibrillation with recorded heart rates of up to 160 beats/min since age 45. He had been unsuccessfully treated with digitalis, disopyramide, propafenone and amiodarone. The ejection fraction by echocardiography was 24%. No family members had hemochromatosis and he had never received blood transfusions. Serum ferritin was 5,430 μg/liter (normal 34 to 310 μg/liter); hemoglobin, 7.4 mmol/liter and potassium 5.1 mmol/liter.

Catheter ablation of the AV junction was performed 1 day after admission. Atrial fibrillation was present. The electrogram of the His bundle measured 0.4 mV (Figure 1). Four shocks were given, but atrial fibrillation returned immediately after ablation. A second session 4 days later, using 6 shocks (300 J each), failed to produce complete heart block. The serum creatine kinase rose to 332 U/liter (3% MB) after the first session and to 365 U/liter after the second. Following the second ablation session, paroxysmal atrial fibrillation was present with episodes of escape beats at 40 beats/min when the pacemaker was turned off. A permanent rate-responsive pacemaker was implanted 3 days after the second ablation session. That same day, however, recurrent episodes of paroxysmal atrial fibrillation with rates of up to 140 beats/min prompted therapy with sotalol (160 mg/day) and digitalis (0.375 mg/day). Electrocardiographic monitoring showed a 3-beat run of ventricular tachycardia (Figure 2A) at 180 beats/min (Holter monitoring before the present admission had revealed ventricular couplets). Continuous monitoring revealed no further ventricular ectopic activity (Figure 2B). No abnormal pacemaker

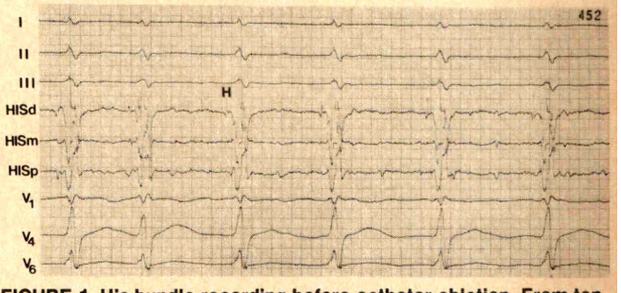

FIGURE 1. His bundle recording before catheter ablation. From top to bottom: standard electrocardiographic leads I, II, III, unipolar recordings from each electrode of a tripolar catheter positioned in the region of the His bundle and precordial leads V_1, V_4, and V_6. The amplitude of the His electrogram measured 0.4 mV and the rhythm is atrial fibrillation.

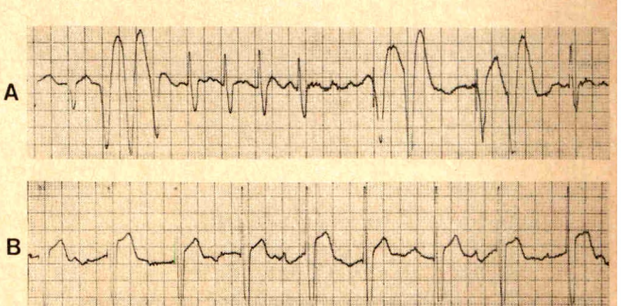

FIGURE 2. *A* shows a 3-beat run of nonsustained ventricular tachycardia, 3 days after catheter ablation. *B* shows sinus rhythm with first-degree atrioventricular block, taken 10 hours before death.

From the Departments of Cardiology and Pathology, University of Limburg, University Hospital, Maastricht, the Netherlands, and the Pathology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received June 8, 1987; revised manuscript received and accepted November 25, 1987.

behavior was observed and electrocardiographic monitoring was discontinued during the evening of his tenth day in the hospital. The patient was found dead in bed 7 hours later.

Necropsy disclosed heavy iron deposits in the liver (weight 2,650 g), spleen (350 g), thyroid gland and pancreas. The heart weighed 530 g. The coronary arteries were normal. Foci of subendocardial hemorrhage were present in the area of the AV bundle. Iron deposits were present in numerous myocardial cells in the walls of all 4 chambers, but heaviest in the left ventricular wall. No grossly visible foci of myocardial necrosis or fibrosis were seen.

A total of 3,140 sections were cut from the AV node and bundle area. Every twentieth section was stained with hematoxylin and eosin, and every two hundredth was stained with Prussian blue. The iron deposits were far less extensive in the conducting tissue than in the "working" myocardium. The myocardial cells in the area of the AV bundle and in the subendocardial portion of the ventricular septum, right ventricular aspect, were lysed and some inflammatory cells were present. The AV node and bundle were intact. The junction between the AV bundle and the right bundle branch was interrupted (Figure 3).

Sudden death has been reported in approximately 2% of patients after catheter ablation.[3] Detailed histopathologic studies have been reported in single patients dying at 6 weeks,[4] 5 months[5] and 5.5 months,[6] respectively, after catheter ablation. Histopathologic changes in patients dying after catheter ablation have shown replacement of AV nodal tissue by fibrous tissue.[4–6] The caudal part of the AV bundle and the bun-

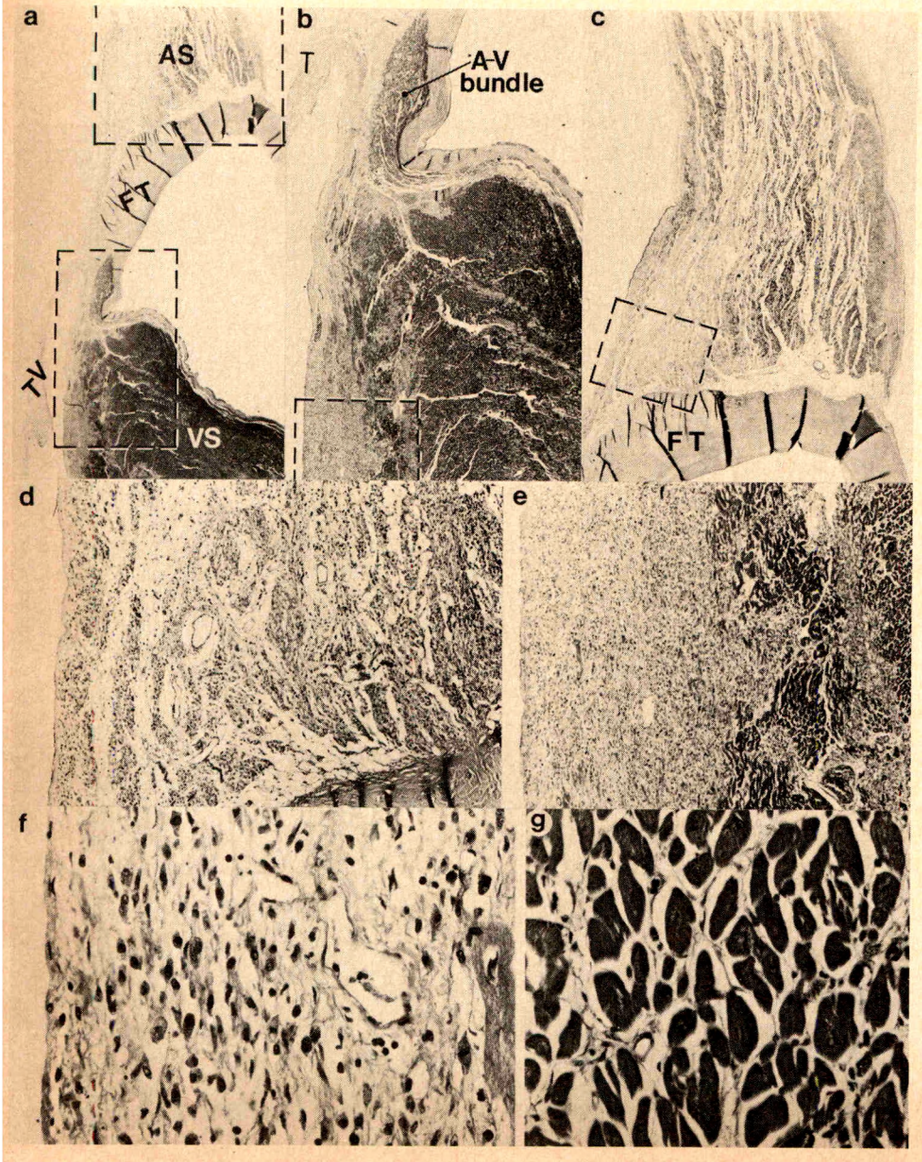

FIGURE 3. Photomicrographs from the area of the atrioventricular (AV) bundle in the patient. All sections were stained by hematoxylin and eosin. *A*, low-power (× 6.5) view of the atrial septum (AS) and the fibrous trigone (FT), within which is the AV bundle and to which is attached the septal leaflet of the tricuspid valve (TV) and the ventricular septum (VS) below. *B*, a closer view (× 16) of one of the areas in brackets shown in *A*. The myocardium beneath the mural endocardium on the right ventricular aspect of the ventricular septum is extensively damaged and a close-up (× 54) of a portion of this damaged myocardium in brackets in *B* is shown in *E*. The connection between the AV bundle and the left bundle branch is intact, but the connection between the AV bundle and the right bundle branch is interrupted. *C*, closer view (× 11.5) of the atrial septum above the fibrous trigone. A portion of this area also is visible in the brackets in *A*. An even closer view (× 54) of the area in brackets in *C* is shown in *D*. The myocardial fibers are extensively damaged. *F*, a high-power view (× 430) of a portion of the damaged myocardial fibers shown in *E*. The myocardial fibers have disappeared. *G*, a high-power view (× 430) of preserved or undamaged myocardium of the ventricular septum for comparison to *F*.

dle branch showed no abnormalities in 2 of the previously reported patients.[5,6] Both had received a single shock (280 J in 1 patient[5] and 275 J in the other[6]). In the report by Bharati et al,[4] the patient received 2 shocks of 500 J each and damage was present in the left and right bundle branch, with scarring seen in the summit of the muscular ventricular septum. In our patient, the AV node was spared and the AV bundle was interrupted at the take-off of the right bundle branch. The continuity of the AV bundle and left bundle branch is in agreement with the symptomatic recurrence of AV conduction in our patient.

The cause of our patient's sudden death is uncertain. Nonsustained ventricular tachycardia occurs occasionally after catheter ablation of the AV junction. Our patient received a new antiarrhythmic agent 3 days before death and its proarrhythmic effect could have contributed to his death.

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Transient Entrainment of Pacemaker Circus Movement Tachycardia

IVO E. KERSSCHOT, MD
PEDRO BRUGADA, MD
KAREL den DULK, MD
WILLEM R.M. DASSEN, PhD
HEIN J.J. WELLENS, MD

The circus movement tachycardia, involving anterograde conduction through the normal atrioventricular (AV) conduction system and retrograde conduction using an accessory AV bypass tract, is 1 of the best understood human models of reentrant tachycardia.[1] The observations made during transient entrainment of many tachycardias[2–6] have supported reentry as the underlying mechanism. In the present report we describe our observations during transient entrainment of pacemaker circus movement tachycardia (PCMT), where the retrograde limb of the circuit is provided by retrograde ventriculoatrial conduction and the anterograde limb by triggering a ventricular pacemaker response to a sensed retrograde P wave. In the first part of the study, entrainment of PCMT is studied in a patient with a DDD pacemaker, whereas an analogous situation is simulated in the second part by a computerized model of the heart's conduction system.

A bipolar dual chamber pacemaker (Medtronic Symbios 7006) was implanted in a 67-year-old man because of symptomatic sinus node dysfunction. The pacemaker was programmed with a short postventricular atrial refractory period of 155 ms, an AV interval of 200 ms and an upper rate limit of 150 beats/min. Sustained episodes of PCMT could be induced after implantation using asynchronous chest wall stimuli. A temporary bipolar pacing lead in the right ventricle was used to study the effects of synchronized overdrive pacing at different pacing rates. The temporary lead tip was located at the lower right ventricular septum, while the ventricular lead tip of the dual chamber pacemaker was in the right ventricular apex.

The effect of ventricular overdrive pacing during PCMT was studied in a computerized model of the conduction system of the heart previously described.[7] DDD pacemaker software was incorporated into the model with the following parameters: lower rate 80/min, upper rate 175/min, AV interval 200 ms, postventricular atrial refractory period 235 ms. Timed premature depolarizations or ventricular pacing at different rates could be programmed at the left ventricular apex in order to initiate or entrain PCMT. The conduction and refractoriness of the different points and segments were analyzed and displayed by a computer at 1-ms intervals.[7] The exact timing of events of interest is referred to in the text and schematically depicted in the corresponding figures, according to absolute timing markers.

The effects of synchronized ventricular pacing during PCMT are shown in Figures 1, 2 and 3. The first 3 ventricular complexes in Figure 1A represent PCMT with a cycle length of 480 ms before overdrive pacing. Arrows 1 and 2 indicate retrograde P waves. The fourth pacing artifact is followed by the fusion of QRS complexes from the pacing pulses of the implanted pacemaker and of the external stimulator which was pacing with a cycle length of 470 ms (arrow 3). This can be explained by the synchronization of the external stimulator to the preceeding ventricular pacing pulse of the implanted pacemaker with a slightly shorter (10 ms) coupling interval than that of the pacemaker. As a consequence, the fourth ventricular complex represents a fusion beat and results in an advancement of the retrograde P wave and subsequent internal pacemaker stimulus (arrow 4). The fifth ventricular complex consists in another fusion morphology, which remains constant during subsequent paced beats except for the last entrained beat (Figure 1B, asterisk), being similar to the native PCMT complex.

From the Department of Cardiology, Clinical Electrophysiology Laboratory, University of Limburg, Annadal Hospital, Maastricht, the Netherlands. Manuscript received April 28, 1987; revised manuscript received November 17, 1987, and accepted November 22.

Figure 2 shows entrainment at a cycle length of 450 ms. The retrograde P wave after the fourth ventricular complex is advanced by means of the same mechanism as that in Figure 1. A look at the QRS morphology shows that the subsequent impulses have a constant and shorter interval between stimulator and pacemaker stimuli in comparison with Figure 1, resulting in a different fusion morphology except, again, for the last entrained beat (Figure 2B, asterisk). Pacing at a cycle length of 440 ms results in the complete inhibition of the implanted pacemaker by the stimulator artifacts (Figure 3), because the stimulator stimuli are delivered before each expected pacemaker stimulus. The last entrained beat (Figure 3B, asterisk) is similar to the native PCMT complex. Further reduction of the pacing cycle length only prolongs retrograde conduction time, as can be appreciated from the last entrained pacing interval, obviously unchanged in ventricular complex morphology (Figure 4A). During pacing at a cycle length of 370 ms, a retrograde conduction block occurs. Now, if any of the burst stimuli is not conducted retrogradely to the atria, the next stimulus will be recognized by the implanted pacemaker as a ventricular premature beat and the postventricular atrial refractory period of the DDD pacemaker will be extended to 400 ms automatically. The subsequent retrograde P wave (if it occurs at all) will not be sensed because it will occur within the atrial refractory period, and the next paced ventricular complex will be recognized as a premature complex again. By this mechanism, the automatic extension of the atrial refractory period can persist to the last paced complex of the burst and PCMT is interrupted (Figure 4B).

The different symbols used subsequently in the computerized model of PCMT are explained in Figure 5A. Figure 5B shows the initiation of PCMT by 2 ventricular premature beats delivered from the left ventricular apex at 3,200 and 3,600 ms. The sensed retrograde atrial activation at time 3,893 ms initiates PCMT with a cycle length of 493 ms and a ventricular complex duration of 90 ms. The panel C of Figure 5 (continuous with panel B), shows the pacing start from the left ventricle with a cycle length of 480 ms at time 5,572 ms. This ventricular beat is a fusion complex, as can be seen from the activation from both stimuli (the first from the overdriving stimulator at the left ventricular apex, the second from the implanted pacemaker at the right ventricular apex). Note that the stimuli from the stimulator, in contrast with our patient model, did not inhibit the DDD pacemaker. The next ventricular complex at 6,039 ms has a different degree of fusion as compared with the previous one, and remains constant from now on. From this point all parts of the tachycardia have the same interval as the entraining pulse train (480 ms). The last entrained pulse at 15,177 ms (asterisk, Figure 5D) shows absence of fusion and is followed by resumption of PCMT at the initial cycle length of 493 ms. The ventricular complex duration during entrainment at a cycle length of 480 ms was 55 ms.

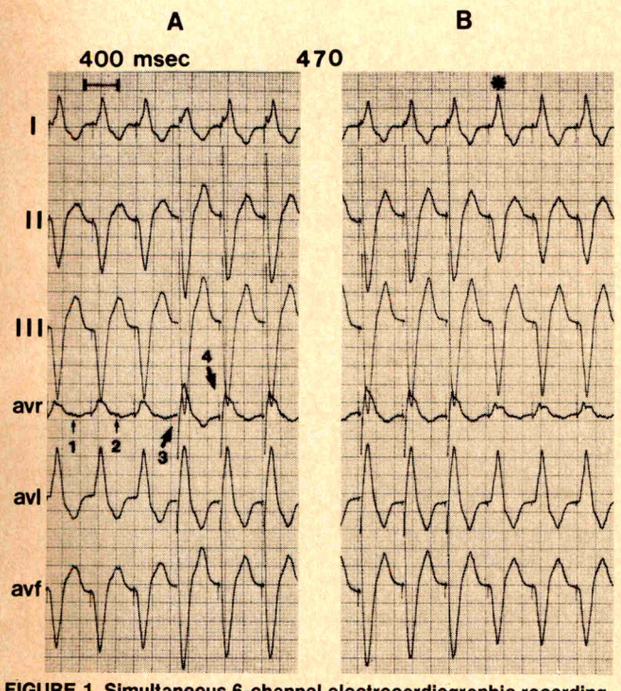

FIGURE 1. Simultaneous 6-channel electrocardiographic recording at the start (*A*) and end (*B*) of overdrive pacing with a cycle length of 470 ms. Pacing artifacts of the implanted pacemaker are best seen in lead I, whereas the large stimuli of the external pacemaker can easily be appreciated in the other leads. The asterisk denotes the last entrained beat occurring at the entrained interval and showing no fusion.

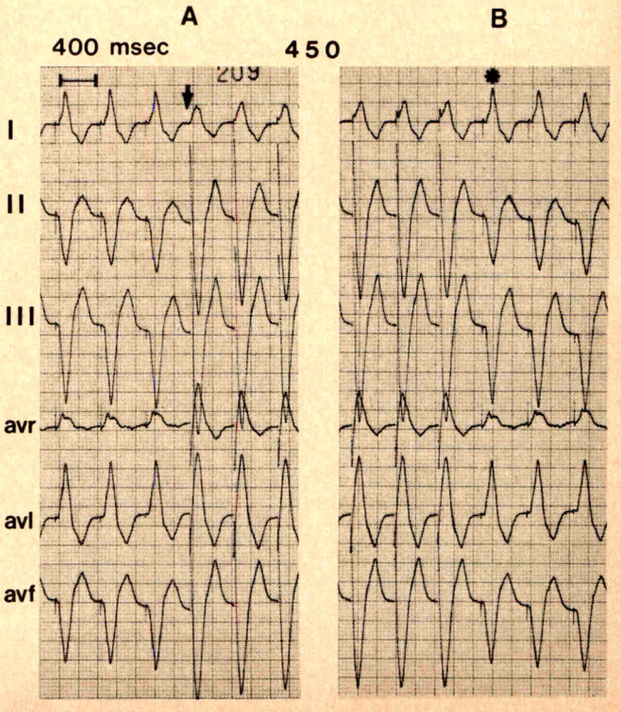

FIGURE 2. Entrainment of PCMT with a pacing cycle length of 450 ms. *Arrow* points to start of overdrive pacing.

Ventricular pacing with a cycle length of 440 ms similarly demonstrates transient entrainment with resumption of the PCMT at the initial rate after sensing the last retrograde P wave (now shown). The ventricular complex duration during pacing at 440 ms was 70 ms.

Ventricular pacing at an interval of 420 ms results in complete inhibition of the internal pacemaker (Figure 5E) because the tissue segment at the right ventricular apex is depolarized by the wavefront from the left ventricular apex (in the computer model the pacemaker is inhibited by the wavefront but not by the stimulation artifact). Furthermore, the tachycardia is interrupted after the last stimulator pulse at 13,405 ms (Figure 5F). Retrograde atrial activity occurred at 13,777 ms (open arrow), and the ventriculoatrial interval, as measured from the stimulator pulse, was therefore 372 ms. The stimulator wavefront from the left ventricle reached the right ventricular apex by conduction at 13,569 ms (i.e., 164 ms later) and only at this time was the pacemaker pulse inhibited and the postventricular atrial refractory period started. The retrograde P wave occurred 208 ms later, during the postventricular atrial refractory period of 235 ms.

Transient entrainment of a tachycardia has been defined as an increase of the tachycardia to a faster

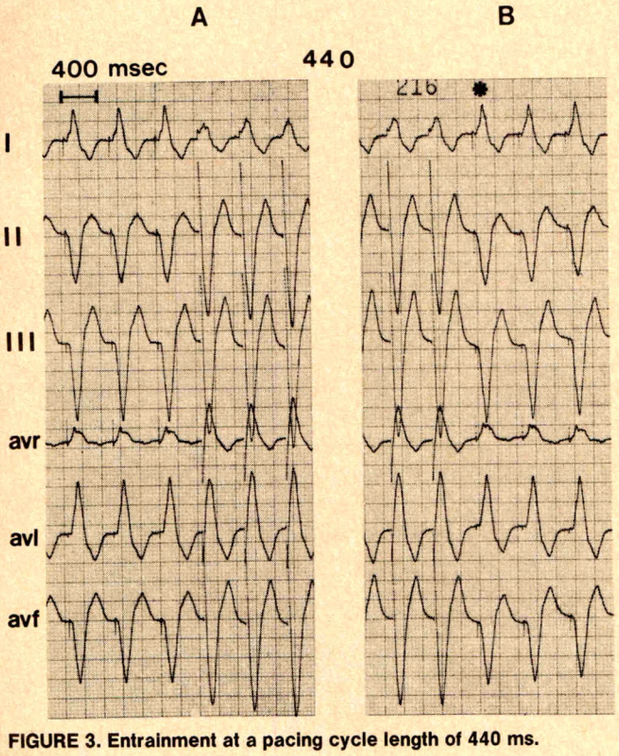

FIGURE 3. Entrainment at a pacing cycle length of 440 ms.

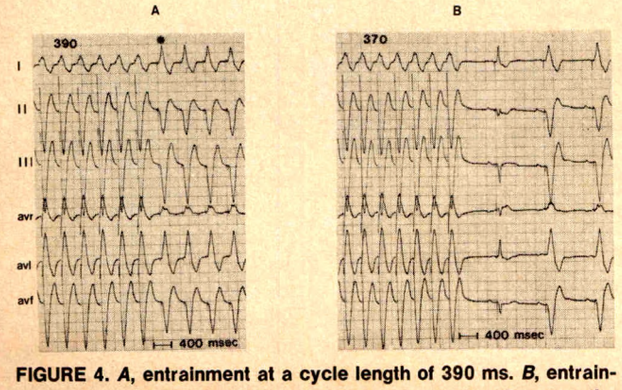

FIGURE 4. *A*, entrainment at a cycle length of 390 ms. *B*, entrainment at a cycle length of 370 ms. PCMT is terminated because the last entrained impulse was not followed by a sensed retrograde P wave.

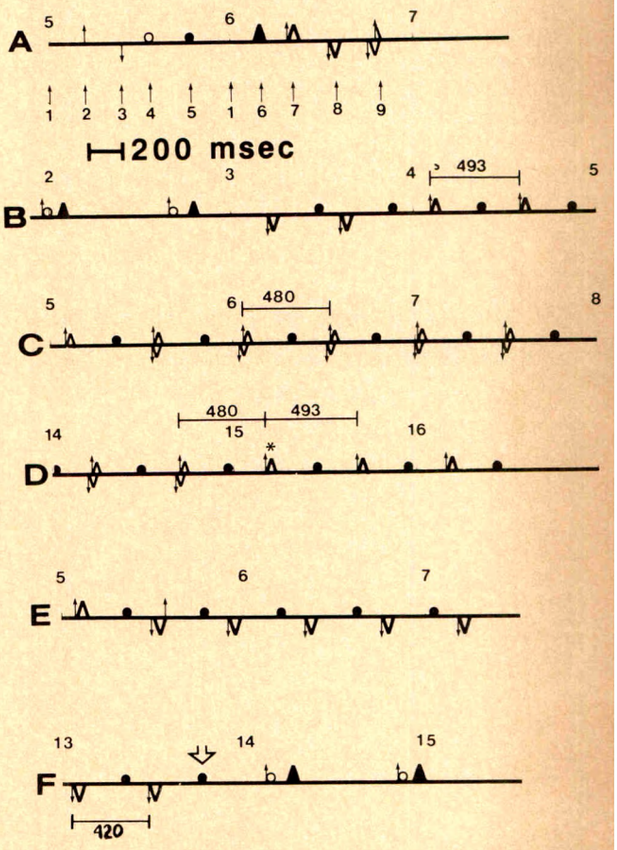

FIGURE 5. *A*, symbols used in subsequent panels to illustrate findings during entrainment of PCMT in the computer model include 1 = absolute timing markers at 1-second intervals; 2 = pacing pulse delivered by the dual chamber pacemaker (either atrial or ventricular); 3 = pacing pulse delivered by the external stimulator; 4 = anterograde atrial depolarization; 5 = retrograde atrial depolarization; 6 = spontaneously conducted ventricular complex; 7 = pacing pulse of the dual chamber pacemaker, followed by ventricular capture; 8 = pacing pulse delivered by the stimulator, followed by ventricular capture; 9 = fusion complex between 7 and 8. *B*, initiation of PCMT by 2 ventricular premature complexes. *C*, entrainment of the tachycardia is started, resulting in an increase in the rate of the tachycardia to the pacing rate. *D*, interruption of pacing and termination of entrainment. The asterisk denotes the last entrained beat, still occurring at the pacing interval. *E*, entrainment of PCMT with pacing at a cycle length of 420 ms. After entrainment, PCMT is interrupted (*F*). The *open arrow* indicates the last entrained P wave, which is not sensed by the atrial amplifier of the pacemaker.

pacing rate, with resumption of the tachycardia at the intrinsic rate upon either abrupt cessation of pacing or slowing of the pacing rate below the rate of the tachycardia.[2-5] Careful observations made during transient entrainment of many tachycardias[2-8] have led to additional criteria: constant fusion during the period of transient entrainment except for the last entrained beat and progressive fusion, consisting of different degrees of fusion at different pacing rates. At a critical rate, localized conduction block followed by activation of that site from a different direction and with a shorter conduction time (as was evident from intracardiac recordings), resulted in interruption of the tachycardia. These findings were most easily explained by reentry as the underlying mechanism of the tachycardia. On the other hand, overdrive pacing during a reentrant tachycardia does not necessarily imply that all the aforementioned criteria will be fulfilled.[8-9] If pacing is performed in close proximity to a small reentrant circuit or just distally to the area of slow conduction in a macroreentrant pathway, it can be anticipated that any fusion at all will be difficult to demonstrate, let alone progressive fusion. Both the PCMT of our patient and the computer model fulfilled the criteria for entrainment.

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Surgical Removal of the Intracoronary Portion of a Fractured Angioplasty Guidewire

LISA C. BACHENHEIMER, MD
CURTIS E. GREEN, MD
DOUGLAS R. ROSING, MD
ROBERT B. WALLACE, MD

Successful percutaneous removal of a foreign body from the aorta and coronary artery has been reported,[1] and surgical removal has been reported in 1 patient.[2] In the latter patient, laceration and dissection of the left anterior descending coronary artery occurred and at operation the wire tip was found to have passed through the arterial wall and into the epicardial fat. Intracoronary wire fracture also has occurred once in our medical center and surgery was required.

A 57-year-old man with unstable angina pectoris underwent cardiac catheterization in August 1984. A 75 to 90% luminal diameter narrowing of the left anterior descending coronary artery proximal to the origin of the first diagonal branch and a 75 to 90% narrowing of the first obtuse marginal branch of the left circumflex coronary artery were found. Percutaneous transluminal angioplasty was performed the next day. The left anterior descending angioplasty was successful with a residual 30% stenosis. With considerable difficulty an 0.014 inch high-torque floppy guidewire (Advanced Cardiovascular System) was then passed across the narrowing in the first obtuse marginal branch, but attempts to advance the balloon dilatation catheter resulted in the distal tip of the guidewire breaking off and remaining coiled within the lumen of this obtuse marginal branch distal to the stenosis (Figure 1). Flow in this artery was poor. Emergency aorto-coronary bypass grafting was performed. On opening the parietal pericardium, the heart appeared normal.

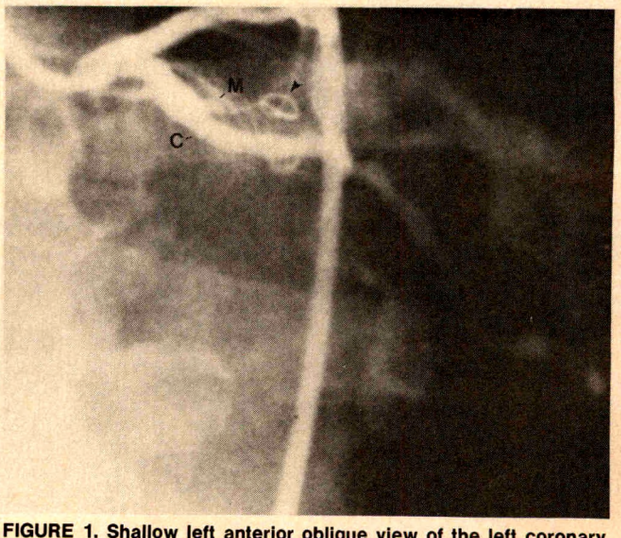

FIGURE 1. Shallow left anterior oblique view of the left coronary artery showing the guidewire (*arrowhead*) coiled in the occluded first obtuse marginal branch (M) of the circumflex coronary artery (C).

From the Departments of Surgery, Radiology and Cardiology, Georgetown University Hospital, Washington, DC 20007. Manuscript received November 6, 1987, and accepted November 13.

Extracorporeal whole body perfusion was established and the patient's core body temperature was lowered to 30°C. A saphenous vein graft was placed from the aorta to the second obtuse marginal. The first obtuse marginal was then exposed proximally and a longitudinal arteriotomy incision was made in it. A thrombus was removed and after extension of the arteriotomy the guidewire was retrieved. The aorto-second obtuse marginal graft was then anastamosed to the first obtuse in a side-to-side fashion. The severe narrowing in the left anterior descending coronary artery also was bypassed using saphenous vein. The patient was rewarmed and weaned from bypass without difficulty. His postoperative course was complicated by a small acute myocardial infarction documented by a peak creatine kinase level of 1,127 IU/liter with an MB fraction of 87 IU/liter. He continues to do well at home 2 years after the cardiac operation.

There have not been enough reported cases of wire fracture to draw any conclusions implicating a particular type of wire as being prone to fracture. In our patient, the wire may have been subjected to increased mechanical stress by being coiled in the artery distal to the severe narrowing. In some cases of wire fracture it may be possible to remove the foreign body without surgery by using a snare.

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Bioprostheses in Tricuspid and Mitral Valve Positions for 100 Months with Heavier Calcific Deposits on the Left-Sided Valve Followed by New Bioprostheses in Both Positions for 95 Months with Heavier Calcific Deposits on the Right-Sided Valve

BENJAMIN N. POTKIN, MD
CHARLES L. McINTOSH, MD, PhD
RICHARD O. CANNON III, MD
WILLIAM C. ROBERTS, MD

Previous reports describing results of simultaneously implanted and explanted bioprostheses in the mitral and aortic valve positions and in the mitral and tricuspid positions usually, but not always, have shown greater degeneration of the bioprostheses in the mitral position than in either the aortic or tricuspid valve position, presumably because of the higher closing pressure on the bioprosthetic cusps in the mitral position.[1-4] Herein, we describe a patient who had simultaneous bioprosthetic replacement of both mitral and tricuspid valves. Later replacement of both bioprostheses revealed heavier calcific deposits on the bioprosthesis in the mitral position after the first bioprosthetic replacement and heavier calcific deposits on the bioprosthesis in the tricuspid valve position after the second bioprosthetic replacement.

From the Pathology, Surgery and Cardiology Branches, National Heart, Lung, and Blood Institute, National Institues of Health, Bethesda, Maryland 20892. Manuscript received October 15, 1987; revised manuscript received and accepted November 13, 1987.

E.V., a 62-year-old white woman with systemic hypertension and diabetes mellitus, had 4 cardiac valve operations (Table I). Congestive heart failure developed during her second pregnancy and 1 year later, at age 35, she underwent closed mitral commissurotomy for mitral stenosis. She was nearly asymptomatic for 2 years thereafter and then congestive heart failure and atrial fibrillation developed. Because of worsening congestive heart failure, at age 46 she had simultaneous replacement of both native mitral and tricuspid valves with Hancock no. 29 and 31 glutaraldehype processed bioprostheses, respectively. She was asymptomatic for the next 8 years when congestive heart failure reappeared at age 54. Left ventricular cineangiogram now demonstrated 4+/4+ mitral regurgitation and a 22 mm Hg mean diastolic pressure gradient across the bioprosthesis in the mitral position. At age 54, the 2 bioprostheses, each of which had been in place for 100 months, were excised along with the diffusely thickened, purely regurgitant aortic valve and all 3 were replaced with Hancock bioprostheses. The excised bioprosthesis in the mitral position had heavier calcific deposits than did the bioprothesis in the tricuspid valve position (Figure 1). Postoperatively, she again was asymptomatic. Catheterization, 7 months later, disclosed a 11 mm Hg mean diastolic pressure gradient across the bioprosthesis in the mitral position. Pulmonary hypertension persisted. Congestive heart failure recurred at age 61 years, 86 months after the last operation. Nine months later or 3 days before death the 3 bioprosthetic valves were replaced because of refractory congestive heart failure. The bioprosthesis that had been in the tricuspid valve position had heavier calcific deposits than that present on the bioprostheses that had been in either the mitral or aortic valve position (Figure 2).

This patient is unique in that 2 prostheses had each been in place for 100 months and 3 other bioprostheses had each been in place for 95 months. When the initially inserted 2 bioprostheses were explanted, heavier

calcific deposits were present in the bioprosthesis that had been in the mitral valve position compared with the one that had been in the tricuspid valve position. When these malfunctioning bioprostheses were excised and replaced with other bioprostheses that were in place for nearly the same amount of time, namely 95 months, heavier calcific deposits developed in the bioprosthesis that had been in the tricuspid valve position compared with that occurring in either bioprosthesis located on the left side of the heart.

The explanation for the reversal of the heavier calcific deposits in the tricuspid and mitral valve positions during the 2 time frames (100 months with the initially inserted bioprostheses and 95 months with the replaced bioprostheses) is unclear. It is likely that during much of the postoperative period after the initial double valve replacement the right ventricular systolic pressure, which represents the closing pressure on the bioprosthesis in the tricuspid valve position, was only mildly elevated (37 mm Hg). In contrast, after the bioprostheses in the tricuspid and mitral valve positions were replaced, the right ventricular systolic pressure remained elevated (65 mm Hg), probably during the entire 95-month period. During this latter 95-month period of high right ventricular systolic pressures, heavier calcific deposits developed on the cusps of the bioprosthesis in the tricuspid valve position than on the cusps of the bioprosthesis in the mitral valve position. The closing pressure, i.e., the left ventricular systolic pressure, on the bioprosthesis in the mitral position, however, was always considerably higher than was the closing pressure on the bioprosthesis in the tricuspid valve position: 160 vs 37 mm Hg after the first

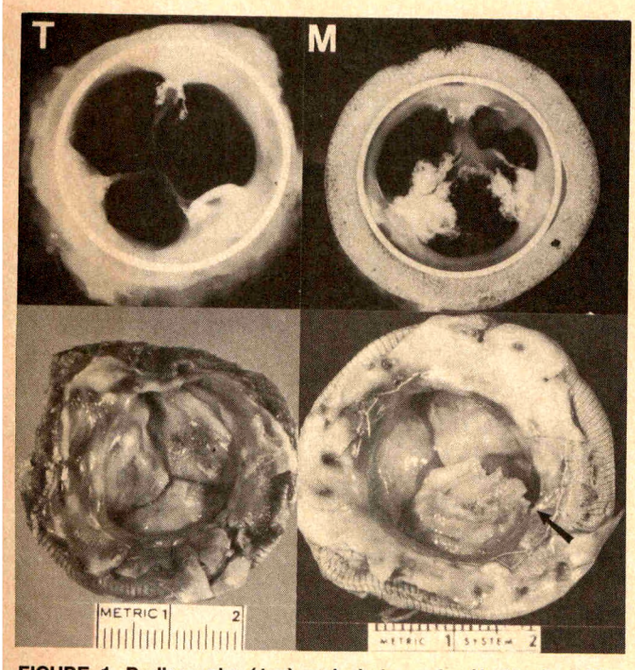

FIGURE 1. Radiographs (*top*) and photographs (*bottom*) of bioprostheses that had been in place in the tricuspid (T) and mitral (M) valve positions for 100 months. Heavier calcific deposits are present in the prosthesis that had been in the mitral valve position. Additionally, 1 cusp of the prosthesis in the mitral position was torn (*arrow*) and this bioprosthesis was severely regurgitant.

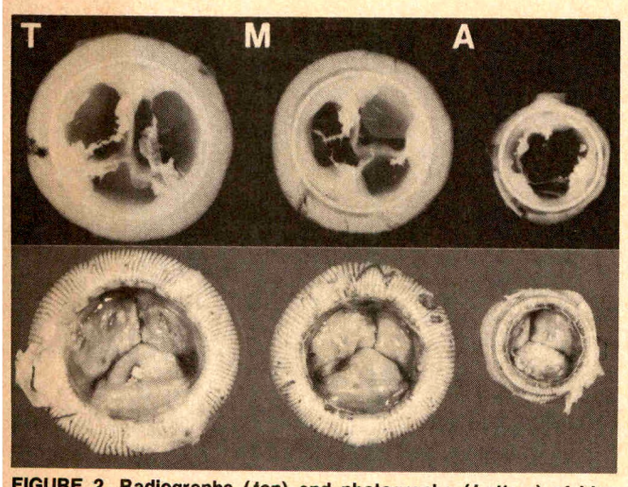

FIGURE 2. Radiographs (*top*) and photographs (*bottom*) of bioprostheses explanted 3 days before death and which had been in place in the tricuspid (T), mitral (M) and aortic (A) valve positions for 95 months. Heavier calcific deposits are present in the bioprosthesis in the tricuspid valve position than in the bioprosthesis in either the mitral or aortic valve positions.

TABLE I Patient's Hemodynamic Data

Month/year	5/1970	8/1971	6/1979	1/1980	8/1986
Age (yr)	45	46	54	55	61
NYHA FC	III	I	III	I	III
SA (s/d)	160/95	150/90	112/70	205/90	137/76
RA V (mean)	25 (18)	14 (10)	26 (22)	16 (13)	22 (20)
RV (s/d)	60/9	37/7	75/16	65/7	67/20
PA (s/d)	60/30	37/20	80/40	65/28	68/28
PAW V (mean)	34 (25)	26 (20)	47 (38)	40 (28)	34 (25)
LV (s/d)	155/16	160/12	117/16	210/25	158/17
CO/CI	5.4/3.1	6.3/3.8	2.2/1.4	5.2/3.3	4.0/2.5
LV-SA psg	0	10	0	5	21
PAW-LV mdg	13	8	22	11	10
RA-RV mdg	6	7	8	7	6
MVA/MVI	*0.8/0.5	2.8/1.7	†	2.1/1.3	1.3/0.8
TVA/TVI	—	2.2/1.3	1.4/0.9	1.4/0.9	1.4/0.9
AR by AA cine (0 to 4+)	0	0	2+/4+	0	1+/4+
MR by LV cine (0 to 4+)	1+/4+	0	4+/4+	0	0

All pressures are in mm Hg. All valve replacements were with Hancock bioprosthesis (size in parenthesis): mitral commissurotomy, 1959; MVR (29) and TVR (31), 2/1971; MVR (27), TVR (31) and AVR (19), 6/1979.

* Calculated valve area underestimated because of mild mitral regurgitation.

† Not possible to calculate valve area because of severe mitral regurgitation.

AA = ascending aorta; AR = aortic regurgitation; AVR = aortic valve replacement; CI = cardiac index (liters/min/m^2); Cine = cineangiography; CO = cardiac output (liters/min); LV = left ventricular; mdg = mean diastolic gradient; MR = mitral regurgitation; MVA = mitral valve area; MVI = mitral valve index; MVR = mitral valve replacement; NYHA FC = New York Heart Association functional class; PA = pulmonary artery; PAW = pulmonary artery wedge pressure; psg = peak systolic gradient; RA = right artial; RV = right ventricular; SA = systemic artery; s/d = systolic/diastolic; TVA = tricuspid valve area; TVI = tricuspid valve index; TVR = tricuspid valve replacement.

valve replacements and 210 vs 65 mm Hg after the bioprosthetic replacements. Thus, factors other than bioprosthetic closing pressures must have played a role in determining which bioprosthesis in the atrioventricular valve positions contained the heavier calcific deposits.

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Left Isomerism with Left-Sided Systemic Venous Return and Ventriculoarterial Concordance: Six-Year Follow-Up After a "Mirror Image" Mustard Operation

SYLVAIN CHAUVAUD, MD
LAURENT FERMONT, MD
DANIELLE BENSASSON, MD
ALAIN CARPENTIER, MD

Left atrial isomerism is usually associated with other complex cardiac abnormalities.[1,2] The atrioventricular connection is ambiguous.[2] When venous returns are inverted and the ventricular arterial connection is concordant, the physiology is that of complete transposition of the great arteries. Surgical correction requires a "modified mirror-image" Mustard procedure. We report a patient who had left atrial isomerism, systemic venous return to the left-sided atrium, partial atrioventricular septal defect, common atrium, azygos continuation of the inferior vena cava and abdominal situs inversus. We emphasize the surgical problems of the mirror image operation regarding venous returns and conductive tissue.

From the Service de Chirurgie Cardiovasculaire, Hôpital Broussais, 96 Rue Didot, 75674 Paris Cedex, France. Manuscript received August 26, 1987; revised manuscript received November 30, 1987, and accepted December 4.

The patient was a 3.5-year-old girl who weighed 14 kg and was cyanotic since birth. No cardiac murmur was present. The liver was situated on the left side and was enlarged. The electrocardiogram disclosed sinus rhythm with first-degree atrioventricular (AV) block (PR interval 0.20 second). Episodes of complete AV block were documented. Chest x-ray showed increased pulmonary vascularity, dextrocardia, a cardiothoracic ratio of 0.67 and a right-sided stomach. Splenic scintigraphy revealed only 1 spleen on the right side. Hemoglobin concentration was 16.3 g/dl. Cardiac catheterizaiton was performed at the age of 24 months. There was an azygos continuation of the inferior vena cava (left sided) to a left superior vena cava. "Right" ventricular and pulmonary pressures were normal. There was complete mixing of oxygenated and deoxygenated blood at the atrial level. Angiocardiography revealed a D-loop with a right-sided and trabeculated ventricle from which the pulmonary artery originated. The subaortic ventricle was morphologically left and left sided. AV valve function was normal on both sides. The aorta was posterior and to the left of the pulmonary artery (Figure 1). Cross-sectional echocardiography demonstrated a common atrium (Figure 2) and an intact ventricular septum. The preoperative diagnosis was situs inversus, ventriculoarterial concordance, common atrium, partial atrioventricular septal defect and intact ventricular septum.

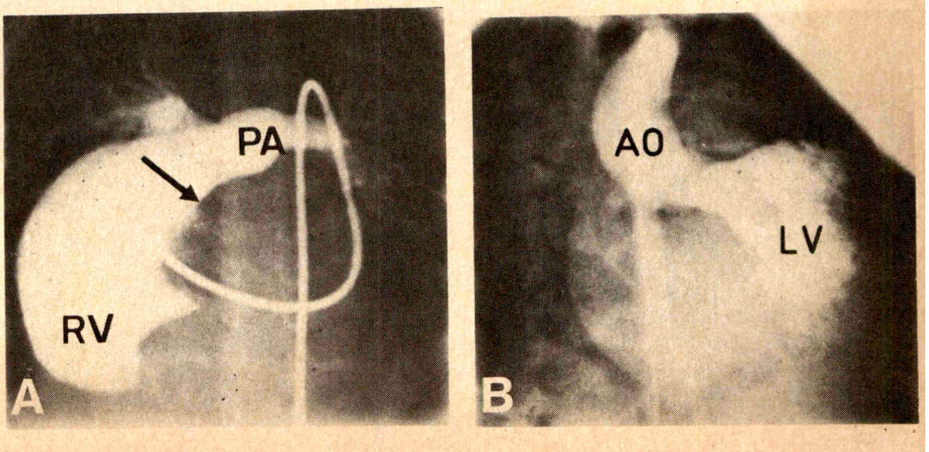

FIGURE 1. *A*, preoperative angiogram with opacification of the right-sided morphologically right ventricle. The catheter is passed in the left inferior vena cava, in the azygos vein and in the left superior vena cava. Ventricular pulmonary discontinuity is shown with an arrow. RV = right ventricle; PA = pulmonary artery. *B*, preoperative angiogram with opacification of the left-sided morphologically left ventricle. Note the deformity of the left ventricular outflow tract, "goose neck," during diastole. LV = left ventricle; AO = aorta.

Surgical repair was performed in May 1981 when the child was 3.5 years old. Extracorporeal circulation was performed between the aorta and 2 venous canulae. The superior venous canula was placed in the superior vena cava. The inferior venous canula was placed in the confluence of the hepatic veins, which were situated on the left side of the atria. Intracardiac lesions were inspected through the appendage situated on the left side. "Left" atriotomy was oblique and directed to the right. There was a left appendage with absence of a crista terminalis, which led to the diagnosis of left atrial isomerism. The atrial septum was absent and a typical partial AV defect was found. An intraatrial transposition of the venous return using a "mirror image" Mustard procedure was performed. A pericardial patch was used such that the superior vena cava and the confluence of the hepatic veins were connected to the tricuspid valve. The coronary sinus was left in to drain into the caval channel. Localization of the His bundle was not performed but superficial stitches were placed in the coronary sinus area (Figure 3). The systemic AV valve was typical of a partial AV defect with a 3-leaflet configuration. The septal commissure was partially closed. The atria receiving the pulmonary veins was enlarged with a pericardial patch. Pressures at the end of the procedure were: mean left atrial 16 mm Hg; mean right atrial 13 mm Hg; aorta 100/50 mm Hg; and pulmonary artery 32/15 mm Hg. The immediate postoperative course was uneventful. AV conduction disturbances remained as they were preoperatively. A permanent pacemaker was inserted on the thirteenth postoperative day with epicardial electrodes. A venous angiogram was performed on the twentieth postoperative day (Figure 4).

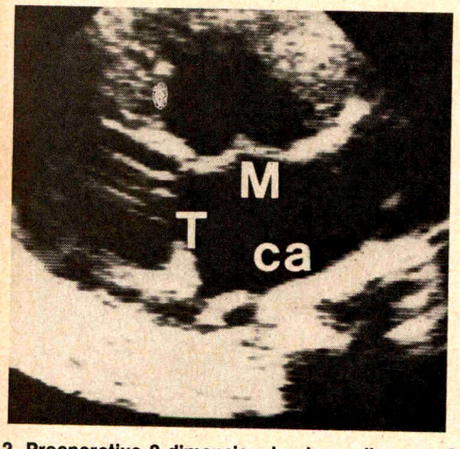

FIGURE 2. Preoperative 2-dimensional echocardiogram. Common atrium is clearly shown. The systemic atrioventricular valve is anterior to the venous atrioventricular valve. Ca = common atrium; M = mitral; T = tricuspid.

Six years after the surgical procedure the child returned for follow-up. Her physical condition was normal; she was not receiving any treatment and had no clinical sign of cardiac failure or valvular incompetence. The heart was still large (cardiothoracic ratio 0.60); pulmonary arterial and venous vascularization were normal. The AV block was still present. The pacemaker and the electrodes were functioning with normal threshold. Cross-sectional echocardiography demonstrated no stenosis of the systemic or pulmonary venous channels and the hepatic veins did not appear to be dilated. The ventricular wall was hypertrophied on both sides. Ventricular function was excellent. The ejection fraction of the systemic ventricle was 62%. The subaortic pathway was normal. On echocardiographic Doppler examination, the "right" AV valve had a trivial incompetence, and the "left" AV valve was normal.

The association of azygos continuation of inferior vena cava, common atrium and left atrial isomerism was pointed out by Macartney et al.[1] In our patient visceral situs was inverted as confirmed by spleen scintigraphy, and polysplenia was excluded. Thoracic situs was not studied with tomography. Atrial situs was much more difficult to establish. Hepatic veins were on the left side of the common atrim leading to the diagnosis of thoracic situs inversus[3] before the opera-

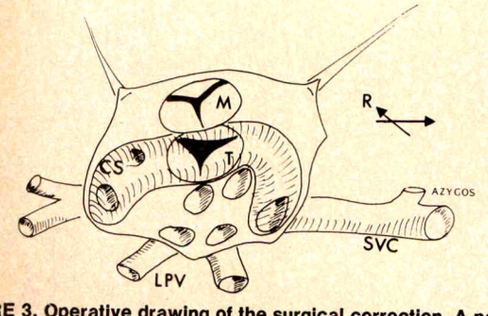

FIGURE 3. Operative drawing of the surgical correction. A pericardial patch is placed in order to connect the orifices of superior vena cava (SVC) and hepatic veins to the tricuspid valve (T). The left atrioventricular valve is typical of a partial atrioventricular defect with 3 leaflets. A partial closure of the commissural cleft was performed. CS = coronary sinus; LPV = left pulmonary veins; M = mitral valve.

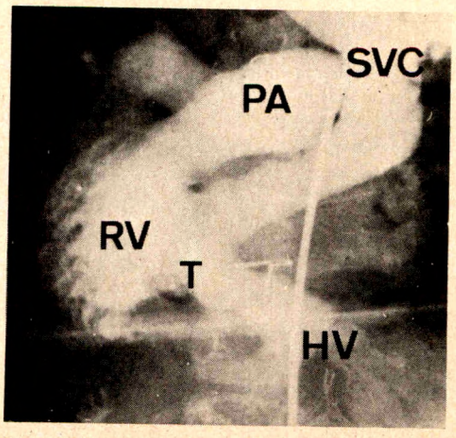

FIGURE 4. Postoperative angiogram of the right chambers. Dye was injected in the superior channel. Opacification of the intraatrial baffle is seen. HV = hepatic veins; other abbreviations as in Figures 1 and 3.

tive examination. Internal morphology of the left appendage revealed a smooth endocardium without a crista terminalis and was of the left atrial type. The presence of left atrial isomerism associated with a common atrium led to the diagnosis of ambiguous AV connection. Surgical correction involved rerouting the systemic venous return to the tricuspid valve. This was achieved with a "mirror image" Mustard operation. The Senning operation was not indicated because of a lack of tissue in the atrial septum.

Localization of the conductive tissue is difficult. Two AV nodes may be present.[4] A similar pattern is found in AV and ventricular discordance (corrected transposition). The posterior node is hypoplastic, and the His bundle originates from the anterior node. Anderson et al[5] showed that the posterior node could be connected with the His bundle. In situs inversus the posterior node is predominant, but not always so. A sling of conductive tissue could be found with fibers around the anterior and posterior margins of the ventricular septal defect.

Uncertainty of the correct location of the conducting tissue explains the high frequency of complete AV dissociation following surgical repair when an AV septal defect is present.[6] Suturing the interatrial baffle into place with a beating heart could help to avoid damage to the His bundle; however, in small patients, as was ours, this can be difficult to achieve.

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Aortic Aneurysms After Subclavian Angioplasty Repair of Coarctation of the Aorta

MONICA M. MARTIN, MD
ROBERT H. BEEKMAN, MD
ALBERT P. ROCCHINI, MD
DENNIS C. CROWLEY, MD
AMNON ROSENTHAL, MD

It has been over 10 years since aortic aneurysms after synthetic patch repair of coarctation of the aorta were first reported. More recent studies suggest that late aneurysm formation after synthetic patch angioplasty may occur in up to 38% of patients.[1,2] These aneurysms typically occur in the aortic wall opposite the synthetic patch, perhaps resulting from stress exerted on abnormal tissue in that portion of the aorta. As is the case with synthetic patch repair, the aortic wall of the coarctation and periductal area is not excised in the subclavian angioplasty procedure. Late aneurysm formation might therefore be expected to occur after subclavian angioplasty as well. In this report we describe 3 children who developed aortic aneurysms following left subclavian angioplasty repair of coarctation.

Case 1: An infant presented during the second week of life with Turner syndrome, congestive heart failure, a discrete thoracic coarctation and severe valvar aortic stenosis. At 12 days of age the coarctation was repaired using the left subclavian angioplasty procedure. An intraluminal web at the site of the coarctation was excised and the subclavian flap was sutured with running 7-0 prolene. At the end of the procedure the patient was normotensive and had no residual coarctation gradient. A surgical aortic valvotomy was performed at 2 months of age. At age 4.5 years a chest x-ray revealed a prominence of the aorta in the area of the coarctation repair (Figure 1). Although an echocardiogram disclosed no abnormality of the aortic

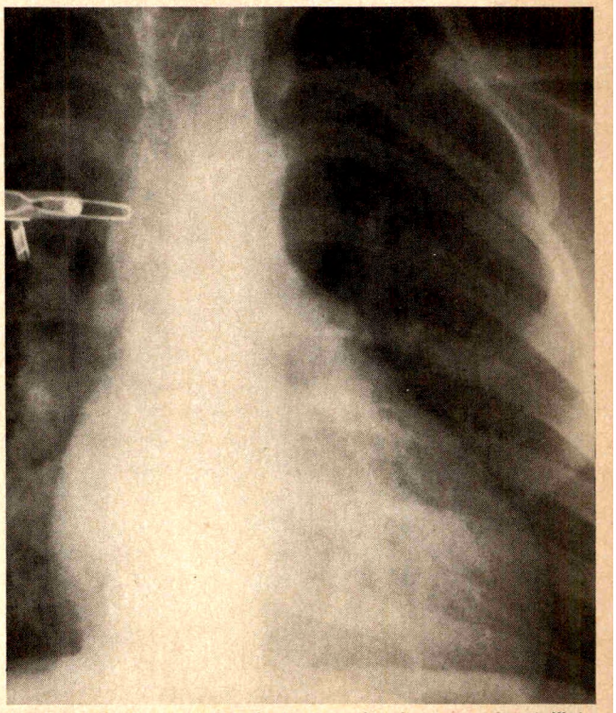

FIGURE 1. Posteroanterior chest x-ray showing a prominent dilatation in the area of prior coarctation repair in a 4.5-year-old asymptomatic girl who had a left subclavian angioplasty procedure at 12 days of age (case 1).

From the Division of Pediatric Cardiology, Department of Pediatrics, C.S. Mott Children's Hospital, University of Michigan, Ann Arbor, Michigan.

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TABLE I Findings After Subclavian Angioplasty Repair of Coarctation of the Aorta

Pt	Age (yrs)	Ratio of Repair to DS Aorta	Aneurysm Extension	Identified by CXR	Identified by Echo
1	4.5	1.5	P,L,M	+	0
2	3	1.6	P,L	0	0
3	2	2.8	A,L,M	+	+

A = anterior; CXR = chest x-ray; DS = descending; L = lateral; M = medial; P = posterior.

FIGURE 2. Anteroposterior left ventricular angiogram demonstrating an aortic aneurysm in a 3-year-old girl who underwent left subclavian angioplasty 21 months earlier (case 2).

arch, a computerized tomographic chest scan suggested the presence of a small aneurysm of the coarctation repair site. A cardiac catheterization revealed aneurysmal dilatation of the repair site, no residual coarctation gradient and mild aortic stenosis. Angiography revealed that the aneurysm diameter was 150% of the aortic diameter at the diaphragm (Table I).

Case 2: A 15-month-old girl presented with heart failure, a severe thoracic coarctation and supravalvar mitral stenosis. The coarctation was repaired with resection of a 3-mm long stenotic segment and end-to-end anastomosis using posterior running and anterior interrupted 7-0 prolene sutures. When an intraoperative residual gradient of 35 mm Hg was noted, a longitudinal incision was made across the anastomosis and a left subclavian angioplasty was performed using running 7-0 prolene sutures. The coarctation gradient was reduced to 5 mm Hg and the patient was normotensive after the operation. A cardiac catheterization at age 3 years revealed an aneurysmal dilatation at the repair site and no residual coarctation gradient. The diameter of the aneurysm by angiography was 160% of the diameter of the aorta at the diaphragm (Figure 2). The aneurysm had not been detected by echocardiogram or chest x-ray.

Case 3: A boy with Taussig-Bing anomaly and discrete thoracic coarctation presented in early infancy with congestive heart failure and cyanosis. At 6 weeks

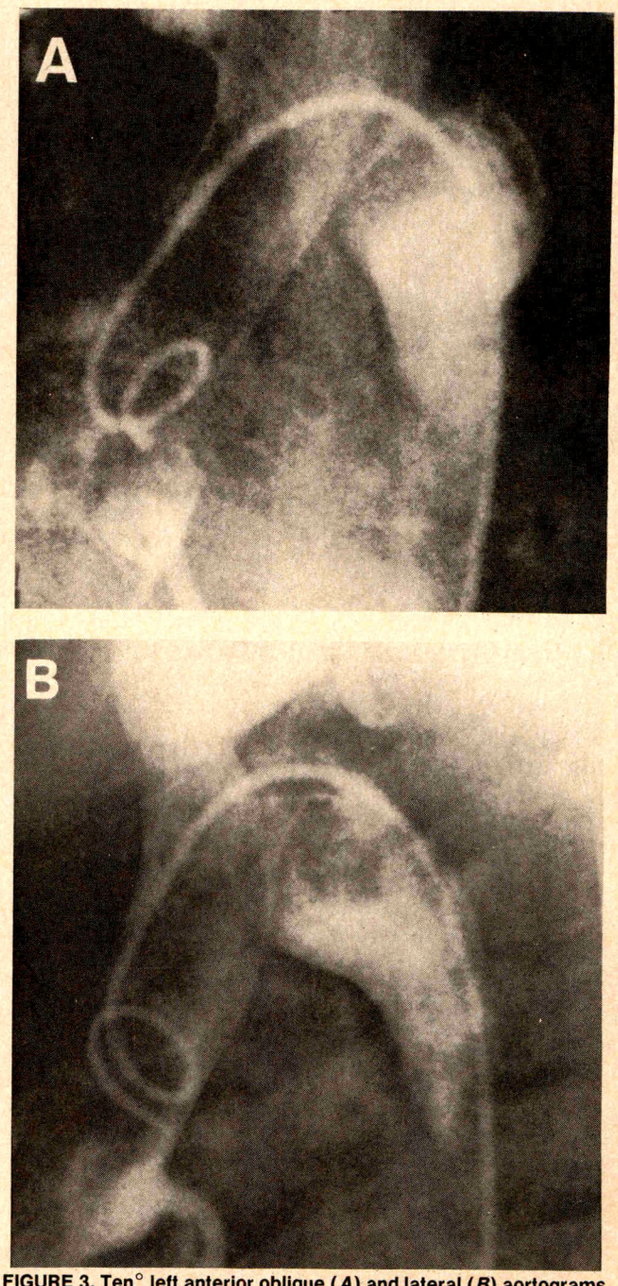

FIGURE 3. Ten° left anterior oblique (*A*) and lateral (*B*) aortograms confirming the presence of a large circumferential aneurysm in a 2-year-old boy who had left subclavian repair of a coarctation at age 6 weeks (case 3).

of age he underwent a left subclavian angioplasty repair of the coarctation and pulmonary artery banding. The subclavian flap was sutured with 7-0 prolene. After the operation there was no residual coarctation gradient and the patient was normotensive. At age 2 years an echocardiogram suggested the presence of an aortic aneurysm and a cardiac catheterization was performed. Angiography revealed aneurysmal dilatation at the coarctation repair site, the diameter of which was 280% of the aortic diameter at the diaphragm (Figure 3). No residual coarctation gradient was present.

Subclavian angioplasty, introduced in 1966 by Waldhausen and Nahrwold,[3] has been recommended by some as the surgical procedure of choice for repair of coarctation of the aorta in infancy. Because the procedure avoids a circumferential suture line and uses viable tissue as a patch, it has been hoped that it would avoid the late problems documented after other types of repair, namely restenosis (after resection and end-to-end anastomosis) and aneurysm formation (after synthetic patch aortoplasty). As long-term follow-up data are acquired, however, the early enthusiasm for the subclavian angioplasty repair may prove to be unwarranted. Recent data suggest that recurrent coarctation may develop more often after subclavian angioplasty than previously suspected.[4] And now, we report instances of aortic aneurysms occurring at the site of a subclavian angioplasty repair.

The synthetic patch aortoplasty technique for coarctation repair was first described by Vosschulte in 1957.[5] As is now the case with subclavian angioplasty, aneurysms occurring at the repair site were not described until nearly 20 years later. In 1976, aortic aneurysms were described in 5 patients from Vosschulte's original series.[6] Late aneurysm formation has since been reported to be as high as 38% after a synthetic patch repair of coarctation.[1,2] Although most of the previous reports have not explicitly defined what constitutes an aneurysm in the absence of pathologic material, fusiform dilatation of the repair site with a diameter ≥150% of the patient's descending aorta correlates well with the presence of an aneurysm.[2] This criterion (comparing the diameter of the dilated vessel to that of the adjacent uninvolved vessel) has also been used to define aneurysms of other muscular arteries as, for example, coronary arteries in Kawasaki disease,[7] and has been applied in the present report.

The mechanism of aneurysmal aortic dilatation after synthetic patch repair of a coarctation may relate to increased tension transmitted by the patch to the more elastic abnormal aortic wall opposite the repair. It was suggested by Moulton in 1983 that late aneurysm formation may be expected regardless of whether the patch is a synthetic material or subclavian artery tissue, since abnormal tissue of the coarctation and periductal area is not excised in either repair.[8] The first aneurysms after subclavian angioplasty have now been documented, lending support to Moulton's concept. It is of interest that in case 2 an aneurysm developed despite coarctation resection before subclavian angioplasty; it may be that a suture line is as vulnerable to excessive wall stress opposite a patch as is native aortic tissue.

Because no patient in this series underwent aneurysm resection, we do not have pathologic data regarding the nature and location of the lesions. We intend to follow these children closely and recommend resection if evidence of progressive aneurysmal dilatation is found. Nevertheless, the clinical data presented indicate that children who have undergone subclavian angioplasty, much the same as those who have had a synthetic patch repair, warrant long-term serial evaluation for possible development of an aneurysm at the coarctation repair site. Long-term studies are necessary to accurately define the incidence and natural history of late aneurysm formation after the subclavian angioplasty procedure.

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Reduction of Nitroglycerin and Isosorbide Dinitrate by Hemodialysis in Refractory Angina Pectoris After Acute Myocardial Infarction

TAKUROH IMAMURA, MD
KAZUO TAMURA, MD
TOSHIFUMI TAGUCHI, MD
MASARU MINODA, MD
MASASHI SEITA, MD

Dosage adjustment of drugs is important to achieve safe and effective therapy in patients undergoing chronic hemodialysis. If drugs are removed by hemodialysis, supplemental drug administration is required to ensure adequate therapeutic plasma levels. Currently, intravenous nitroglycerin[1] and oral administration of isosorbide dinitrate[2] are commonly used in patients with coronary artery disease. However, there are no available pharmacokinetic data of these drugs in patients who undergo hemodialysis. We describe a patient with refractory angina after acute myocardial infarction whose plasma nitroglycerin and isosorbide dinitrate concentrations were measured during hemodialysis.

A 43-year-old man, who had been on hemodialysis for 3 years, was transferred to our hospital on January 14, 1986, because of retrosternal chest pain that had persisted over 17 hours before admission. The electrocardiogram showed anteroseptal myocardial infarction. Hemodynamic study demonstrated elevated mean pulmonary artery wedge (35 mm Hg) and pulmonary artery pressures (38/28 mm Hg), and normal cardiac index (4.0 liters/min/m²). Nitroglycerin, sustained-release isosorbide dinitrate and diltiazem were started soon after he was placed in the coronary care unit. Chest pain at the time of admission was soon relieved with this treatment. However, anginal attacks occurred frequently, especially during hemodialysis, despite stable blood pressure and heart rate. During the anginal attacks electrocardiogram showed ST-segment elevations associated with peaked T' waves in anterior precordial leads.

Hemodialysis was performed 4 times a week using hollow fiber dialyzers, RENAK-A 10M (Kawasumi Laboratories, Inc.) containing cellulose acetate membranes of 11 μ. It was usually started around 9:00 A.M. and lasted 4 hours. Blood samples were obtained from the inflow and outflow portions of the hemodialysis system to measure plasma nitroglycerin and isosorbide dinitrate concentrations. Blood flow was maintained at about 150 ml/min and transmembrane pressure at about 250 mm Hg throughout hemodialysis unless hypotension or profound general weakness developed. On the thirty-fifth hospital day, blood samples were obtained at 9:30 and 11:00 A.M. and 1:00 P.M., i.e., 30 minutes, 120 minutes and 240 minutes after hemodialysis was started, respectively. Intravenous nitroglycerin was infused at a rate of 100 μg/min into the right atrium through a Swan-Ganz catheter. Sustained-release isosorbide dinitrate, 40 mg, and diltiazem, 90 mg, were given by mouth every 6 hours starting at 6:00 A.M. Nitroglycerin concentrations in the dialysates were also measured at the same time (Table I). This demonstrated a 16 to 29% reduction in plasma nitroglycerin concentrations after transit of the blood through the dialyzer. The plasma isosorbide dinitrate concentrations were more significantly reduced by 44 to 60% after the blood was dialyzed (Table II). Despite oral administration of isosorbide dinitrate at noon, the plasma isosorbide dinitrate level at 1 P.M. (240 minutes on dialysis) was low. A possible explanation for this low concentration is that the isosorbide dinitrate used in this patient was a sustained-release preparation and, therefore, plasma concentration might not have increased sufficiently 60 minutes after the last dose of isosorbide dinitrate was given. The nitroglycerin and isosorbide dinitrate concentration assays were performed by gas-chromatography mass spectrometer JMS-DX300 (JEOL) and gas-chromatography 9AM (Shimadzu), respectively.

Subsequently coronary arteriography was performed showing a 99% diameter stenosis in the proximal portion of the left anterior descending coronary artery and a 75% diameter stenosis in the left circumflex coronary artery. The right coronary artery was normal. Left ventriculography demonstrated anteroseptal wall hypokinesis. Percutaneous transluminal

TABLE I Nitroglycerin Concentration (Infusion Rate of 100 μg/min)

Time after the Start of HD (min)	NTG Concentration (ng/ml)			Extraction (%)
	Inflow	Outflow	Dialysate	
30	49	35	5.6	29
120	58	49	7.9	16
240	56	42	7.4	25

Extraction = (inflow − outflow)/inflow × 100.
HD = hemodialysis; Inflow = inflow portion of the dialyzer; NTG = nitroglycerin; Outflow = outflow portion of the dialyzer.

TABLE II Isosorbide Dinitrate Concentration

Time after the Start of HD (min)	Time after the Last Dose of ISDN (min)	ISDN Concentration (ng/ml)			Extraction (%)
		Inflow	Outflow	Dialysate	
30	210	87	49	8.4	44
120	300	56	31	4.0	44
240	60	51	20	4.7	60

ISDN = isosorbide dinitrate; other abbreviations as in Table I.

From the Department of Internal Medicine and Urology, Miyazaki Prefectural Hospital, 5-30 Kitatakamatsu-cho, Miyazaki, 880, Japan. Manuscript received April 21, 1987; revised manuscript received and accepted December 14, 1987.

Dr. Imamura's present address: The First Department of Internal Medicine, Miyazaki Medical College, 5200 Kihara Kiyotake, Miyazaki 889-16, Japan.

angioplasty or coronary artery bypass surgery was recommended, but the patient was not willing to undergo these procedures. Doses of isosorbide dinitrate and diltiazem were increased to 200 mg and 450 mg, respectively. In addition, propranolol was added, but it had to be discontinued because of profound hypotension during hemodialysis. Although we were able to gradually decrease the dose of intravenous nitroglycerin, it was still required to control the patient's anginal attack during hemodialysis. It took 3 months to withdraw the patient from intravenous nitroglycerin during hemodialysis. Subsequently his anginal attacks were controlled with oral medications. He was discharged home and has been doing well under outpatient hemodialysis without intravenous nitroglycerin.

Nitroglycerin and isosorbide dinitrate were dialyzed by hemodialysis. The molecular weights of nitroglycerin and isosorbide dinitrate are 227.09 and 236.14, respectively. These are small enough to pass through a semipermeable membrane of the dialyzer. Nitroglycerin[3] and isosorbide dinitrate[4] are reported to be bound to the polyvinyl chloride tubes used in intravenous infusion sets, and the loss of the drugs appeared to be dependent on the flow rate. Although polyvinyl chloride tubes are used in this hemodialysis system, blood flow is so fast that binding of nitrate to these tubes may be negligible. This is suggested by the fact that significant amounts of nitrate were found in the dialysates, although the possibility of binding nitrate to the tubes and the dialyzer could not be completely ruled out. It has been reported that diltiazem is not removed by hemodialysis.[5] In summary, various factors, including the reduction of plasma nitroglycerin and isosorbide dinitrate concentration by hemodialysis, may precipitate myocardial ischemia during hemodialysis. The dosage of these agents must be adjusted to maintain therapeutic plasma concentrations.

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Reversal of ST Depression and Low Maximal Oxygen Uptake After Verapamil with Normal Coronary Arteries and Pulmonary Disease

ILEANA L. PINA, MD
ELIZABETH V. SMITH, RN
MERCEDES FUGUET, CVT
HORST J. BAIER, MD
ROBERT J. MYERBURG, MD

Exercise-induced ST-segment depression in the absence of coronary artery disease has been described in many conditions and circumstances, such as digitalis use, electrolyte abnormalities, left ventricular hypertrophy and cardiomyopathy.[1] The present report describes ST depression and ventricular arrhythmias in a patient free of coronary artery disease but with pulmonary disease.

A 58-year-old man presented with recent onset of angina on exertion without concomitant dyspnea. He had been in good health, had no prior history of systemic hypertension, diabetes mellitus or heart disease and was not receiving medication. The patient had a history of cigarette smoking (30 packs/year), had worked as a window and glass door installer and was accustomed to heavy labor. His blood pressure was 140/70 mm Hg and his heart rate 60 beats/min with regular rhythm. The lungs were clear and an S_4 gallop was audible at the apex. The resting electrocardiogram was normal.

A treadmill exercise test with thallium scintigraphy was performed using a Bruce protocol (test 1). At 7 minutes of exercise, 3 mm of horizontal ST depression was recorded in leads II, III, aVF, V_5 and V_6 and ventricular ectopy developed in patterns of triplets and couplets. The ST changes lasted 10 minutes into recovery (Figure 1). Thallium imaging demonstrated normal perfusion. Coronary angiography revealed normal coronary arteries. Pulmonary function testing was compatible with moderate hypoxemia at rest (pO_2 65.5 mm Hg) and mild obstructive changes. A repeat exercise test (test 2) was performed using a Medical Graphics 2001 metabolic cart. At 9 minutes, the patient developed chest pressure and diffuse wheezing. Exer-

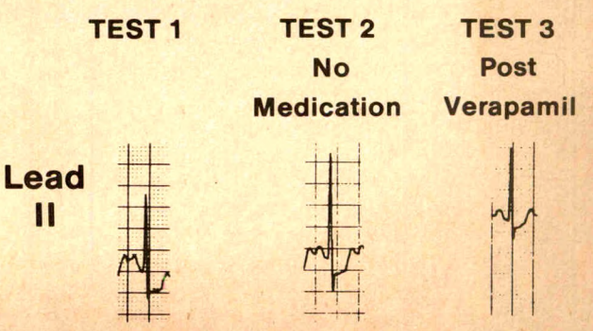

FIGURE 1. Representative QRS (lead II) with ST-segment changes.

From the Division of Cardiology, University of Miami School of Medicine, Miami, Florida. Manuscript received August 28, 1987; revised manuscript received December 3, 1987, and accepted December 4.

Dr. Pina's present address: Hahnemann University, Cardiac Fitness Center, Broad and Vine, MS 110, Philadelphia, Pennsylvania 19102-1192.

TABLE I Exercise Hemodynamics Before and After Verapamil

	Before	After
Duration (min)	9.0	9.0
Rest standing heart rate (beats/min)	74	65
3-minute heart rate	105	90
6-minute heart rate	123	108
Peak heart rate (9 minutes)	154	142
Predicted maximum heart rate (%)	96	89
Rest standing blood pressure (mm Hg)	125/70	110/80
3-minute blood pressure	160/80	120/75
6-minute blood pressure	185/76	140/76
Peak blood pressure (9 minutes)	190/78	170/95
Double product-peak exercise*	29.26	24.14
Double product-onset ST depression*	16.0	22.6
VO_2 Max (ml/min)	1,666	2,267 ($p < 0.001$)
VO_2 Max/kg (ml/min/kg)	21 (6 MET)	29 (8 MET)
O_2 pulse (VO_2/max HR) (ml)	10	16

* Double product expressed as beats-mm Hg/min × 1,000.
HR = heart rate; MET = 3.5 ml oxygen uptake/min/kg; VO_2 max = peak oxygen uptake.

cise hemodynamics are shown in Table I. Peak O_2 uptake was 1.66 liter/min with an O_2 pulse of 10, and a peak double product of 29.26 × 10^3 beats-mm Hg/min. The ST depression noted previously was reproduced (Figure 1) with an onset at a double product of 16.0 × 10^3 beats-mm Hg/min. One hour after the oral administration of 80 mg of verapamil, the exercise test was repeated in the same manner (test 3). At 9 minutes, peak O_2 uptake was 2.27 liter/min with an O_2 pulse of 16 and a peak double product of 24.14 × 10^3 beats-mm Hg/min. There was no evidence of exercise-induced wheezing. Upsloping ST depression (onset at a double product of 22.6 × 10^3 beats-mm Hg/min) of 1 mm was recorded at peak exercise, returning to baseline 4 minutes into recovery.

The ST-segment depression with exercise was horizontal, lasted 10 minutes in recovery and was accompanied by symptoms and ventricular arrhythmias. Peak O_2 uptake was low. The patient lacked any other condition or circumstance generally associated with ST depression representing a false-positive test for ischemia. Improvement after verapamil prompts several hypotheses.

Because hypoxemia was present at rest, a further decrease in pO_2 would account for exercise-induced ischemia. Kurihara et al[2] predicted pO_2 during exercise in patients with chronic pulmonary disease using diffusing capacity and a known peak O_2 uptake and found a high correlation with actual measurements of pO_2. With this formula, our patient would have a pO_2 of >100 mm Hg. To further corroborate this, we employed ear oximetry during exercise and found no evidence of desaturation.

Henriquez et al[3] found that patients with chronic bronchitis and severe exercise intolerance (VO_2 max <2.1 liter/min) had elevated pulmonary resistance at rest, with the highest values in those subjects whose O_2 pulse was <11 ml and whose maximal heart rate was >95% predicted. ST depression may represent right ventricular pressure overload to high pulmonary resistances. Calcium antagonists can dilate the pulmonary vascular bed[4] and inhibit exercise-induced bronchospasm.[5,6]

Finally, a defective subendocardial vasoregulatory system could account for microscopic (albeit electrocardiographically significant) ischemia not detected grossly by thallium scintigraphy. Inadequate coronary vasodilator responses in patients with normal coronary arteries have been described.[7] Moreover, calcium antagonists have reduced angina frequency and improved exercise tolerance in such patients.[8] Exercise duration was unchanged in our patient. A more significant change, i.e., an increase in maximal O_2 uptake at a lower heart rate, occurred after verapamil administration, which implies improvement in stroke volume because maximal A-V O_2 difference is physiologically limited to 15 to 17 vol%.[1] The onset of ST depression occurred at a higher double product suggesting an increase in flow. In the absence of physical training, these changes can only be attributed to the effect of verapamil. At this time it could not be determined whether improvement in vasoregulation or enhancement of ventricular relaxation produced the changes described.

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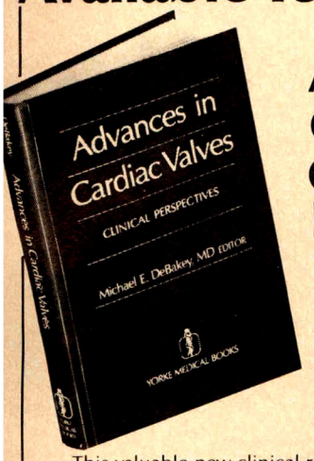

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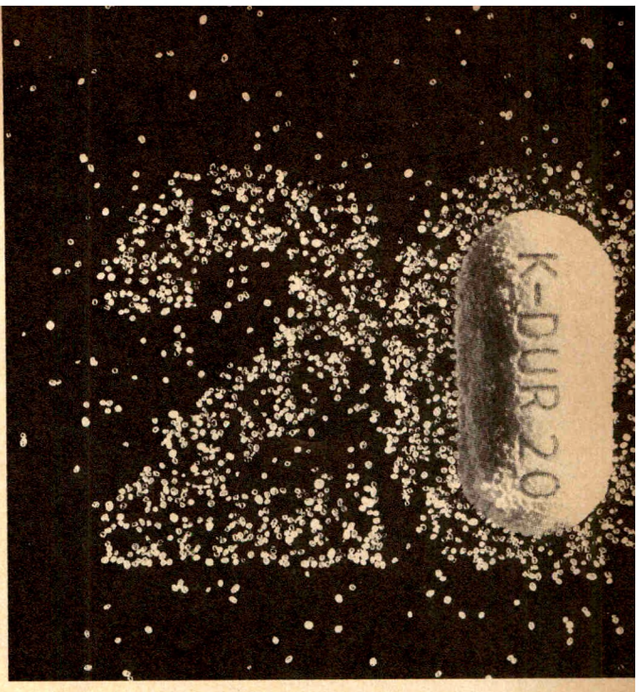

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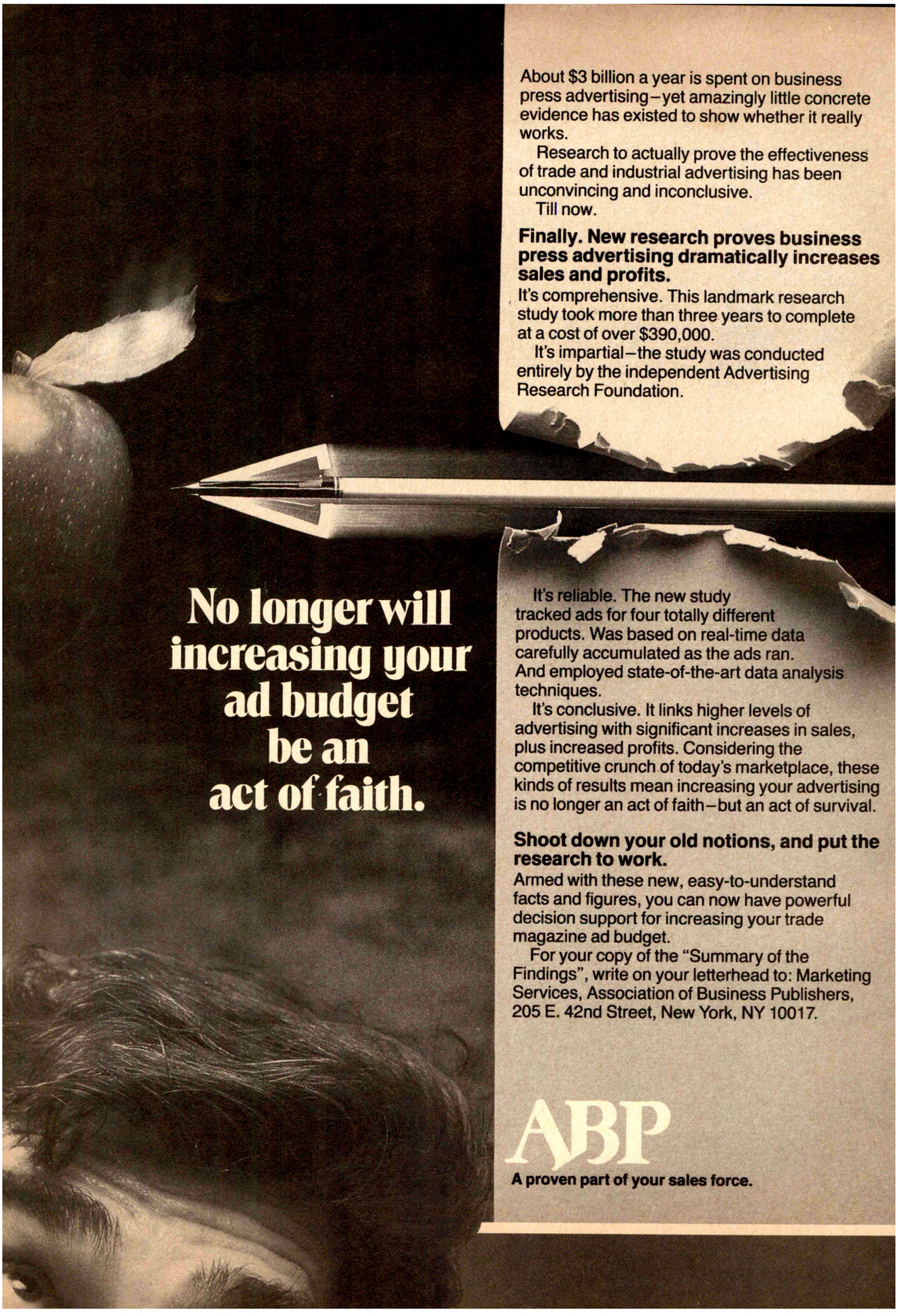

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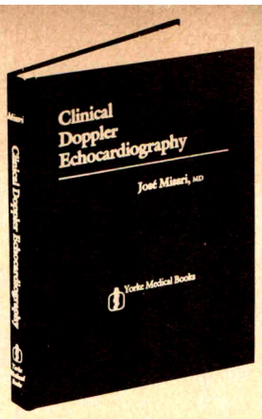

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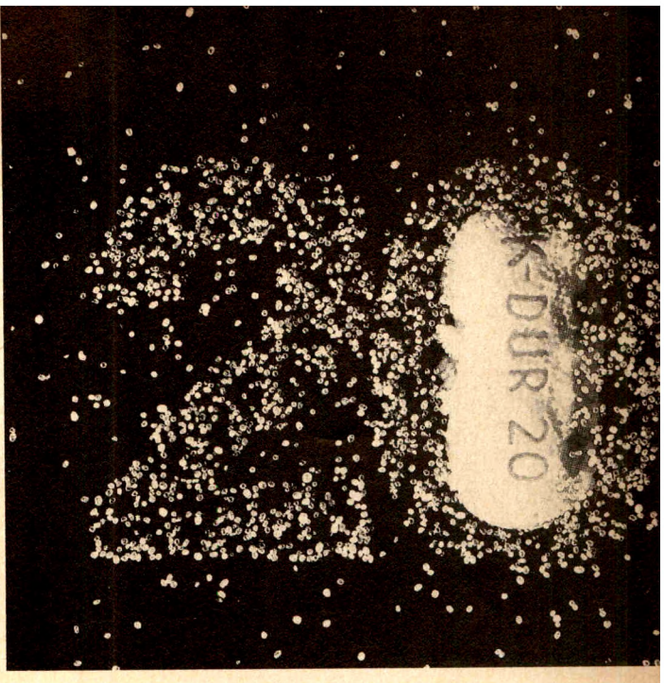

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3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

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Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

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WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

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Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS.**

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Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE).** There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS);** other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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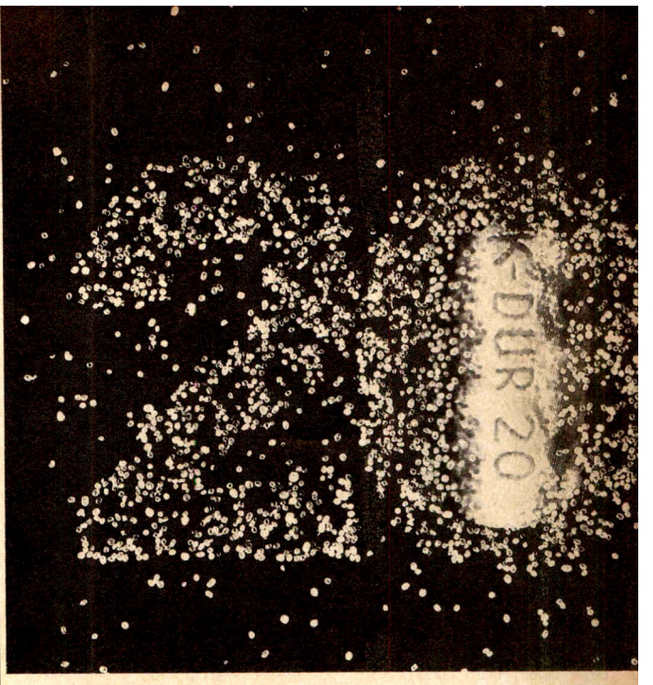

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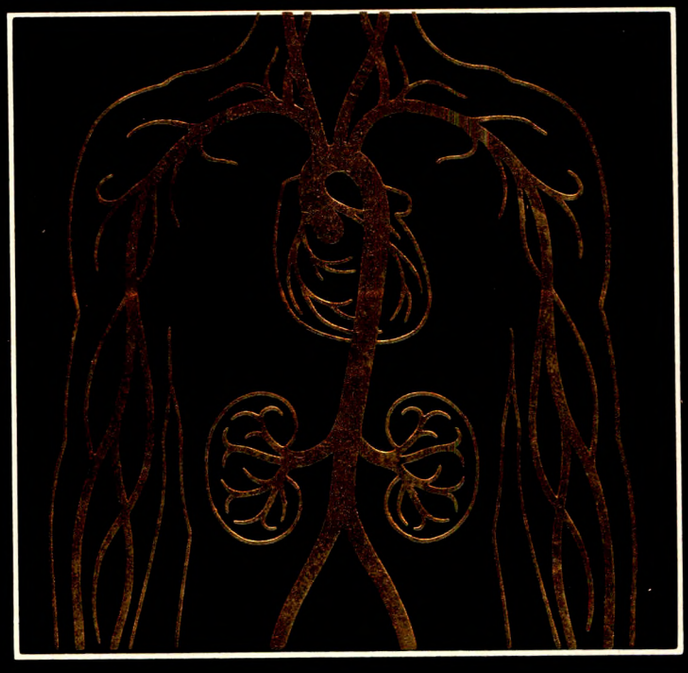

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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure<90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present).

Warnings: Verapamil should be avoided in patients with severe left ventricular dysfunction (eg, ejection fraction<30%) or moderate to severe symptoms of cardiac failure and in patients with significant ventricular dysfunction if they are receiving a beta-adrenergic blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce a decrease in blood pressure below normal levels, which may result in dizziness or symptomatic hypotension. Elevations of liver enzymes have been reported. Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). The effect of verapamil on AV conduction and the SA node may cause asymptomatic 1st-degree AV block and transient bradycardia, sometimes with nodal escape rhythms. PR-interval prolongation is correlated with verapamil plasma concentrations especially during initial titration. Higher degrees of AV block are infrequent (0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Studies in a small number of patients suggest that concomitant use of Calan and oral beta-adrenergic blockers may be beneficial in certain patients with chronic stable angina or hypertension. Combined therapy can also have adverse effects on cardiac function; therefore patients should be closely monitored. A decrease in metoprolol clearance may occur with concurrent use of verapamil and metoprolol. Chronic verapamil treatment increases serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when verapamil is given, and the patient reassessed. Verapamil used concomitantly with oral antihypertensive agents will usually have an additive effect on lowering blood pressure that in some cases may be excessive; therefore patients should be monitored appropriately. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Until further data are obtained, combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Quinidine levels may increase during verapamil therapy. Clearance of verapamil may be reduced in concomitant use with cimetidine. Concomitant use of verapamil and lithium may result in decreased serum lithium levels. Verapamil therapy may increase carbamazepine concentrations during combined use. Therapy with rifampin may markedly reduce oral verapamil bioavailability. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Another study in rats showed no evidence of carcinogenicity. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy in children under 18 have not been established.

Adverse Reactions— oral verapamil: Constipation (8.4%), dizziness (3.5%), nausea (2.7%), hypotension (2.5%), edema (2.1%), headache (1.9%), CHF/pulmonary edema (1.8%), fatigue (1.7%), bradycardia: HR <50/min (1.4%), AV block: total 1°, 2°, 3° (1.3%)/3rd-degree (0.8%), flushing (0.1%); elevations of liver enzymes have been reported (see *Warnings*). The following reactions, reported in 1.0% or less of patients, occurred under circumstances where a causal relationship is not certain: angina pectoris, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, dyspnea, arthralgia, rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, blurred vision, gynecomastia, impotence, increased urination, spotty menstruation.

1/12/87 • 7W107V

Address medical inquiries to:
G.D. Searle & Co.
Medical Communications Department
Box 5110, Chicago, IL 60680

SEARLE Searle & Co.
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Journal: Harvey W, Heberden W, Withering W, Stokes W, Murrell W, Einthoven W, Osler W. Anomalies and curiosities of cardiology and of cardiologists. Reflections of famous medical Williams. Am J Cardiol 1984;53:900–915.

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LETTERS*

TERMINATION OF VENTRICULAR TACHYCARDIA WITH TRANSCUTANEOUS CARDIAC PACING

The case report by Rosenthal et al,[1] which reported on the termination of ventricular tachycardia (VT) with transcutaneous pacing, is similar to our previous publication.[2] Several additional points should be made.

The termination of VT with transcutaneous pacing is limited by the patient's stability and the type of transcutaneous pacemaker. Transcutaneous pacing's advantage over low energy cardioversion is that anesthesia can be avoided. For the unconscious patient the best method is low energy cardioversion. Transcutaneous pacing is best used for the conscious patient whose VT rate is slow, who has not responded to simple medical therapy such as intravenous lidocaine and in whom a transvenous wire is not in place. The Zoll transcutaneous pacemaker's maximum pacing rate is 180/min,[1] which limits overdrive transcutaneous termination with this pacemaker to VTs with a rate below 160 beats/min. This limitation is not common to all transcutaneous pacemakers, however, as our pacemaker (Transpace, model 25, Micromedical Devices Inc.) paces up to rates of 300/min.

The largest population of conscious patients, who require an intervention to terminate a fast heart rhythm, are those with supraventricular tachycardia. Transcutaneous pacing appears to affect atrial rhythm, as illustrated in our case,[2] where a short period of an irregular supraventricular rhythm followed the termination of the patient's VT with transcutaneous pacing. The possible danger of inducing rapidly conducting atrial fibrillation in a patient with an accessory pathway is remote and is easily corrected with an electrical cardioverter. VT or ventricular fibrillation might also be induced, and again, should respond quickly to cardioversion. The danger of inducing a ventricular arrhythmia could be decreased by using R-wave triggered pacing (DVT mode[3]). Simultaneous transvenous atrial and ventricular pacing is used to treat patients with recurrent supraventricular tachycardia,[4] and simultaneously transcutaneous pacing will probably terminate some forms of supraventricular tachycardia.

Transcutaneous pacing could prove to be fast, simple and safe for the termination of tachyarrhythmias, especially supraventricular tachycardia. In addition to higher rates, transcutaneous pacemakers should provide new synchronization modes to suit them to tachycardia termination. Research should be done to determine the optimal positions for the pacing electrodes and the safest and most effective pacing protocols for transcutaneous pacing termination of tachycardias.

Michael D. Rosengarten, MD
Montreal, Canada
27 October 1986

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FETAL DOPPLER ECHOCARDIOGRAPHY

I read with interest the article by Hata et al,[1] who performed 65 continuous-wave Doppler ultrasonographic examinations on 57 normal fetuses. Their experience was similar to previously published data.[2,3] However, I object to the use of continuous-wave ultrasound particularly in normal fetuses because continuous-wave Doppler exposes the fetus to higher intensities of ultrasound energy than the pulse-wave mode. This, coupled with loss of range resolution makes it less favorable for use in normal fetuses especially since maximal velocities recorded are still within the range of the pulse-Doppler technique. Moreover, the Aloka SSD-730 system used by the investigators allows for either pulsed or continuous-wave Doppler modes. Thus, it is prudent and probably safer to use pulse-wave Doppler techniques in fetal studies in general and in normal fetuses in particular and limit the energy output of the system to the minimum necessary for adequate examination with signal intensity usually maintained at or below 100 mW/cm^2. The continuous-wave modality should be reserved for occasional use only and in selected cases.

Edward G. Abinader MD, FRCPI
Haifa, Israel
24 April 1987

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REPLY: We also think that it is prudent and probably safer to use the Doppler equipment with low signal intensity in fetal studies. An Aloka SSD-730 used in our study is applicable for either pulsed or continuous-wave modes. In the continuous-wave Doppler mode, the spatial average-temporal average (SATA) intensity was 24 mW/cm^2, and the spatial peak temporal average (SPTA) intensity 120 mW/cm^2. Therefore, the SATA intensity was within the limited value of theFDA (94 mW/cm^2), and the SPTA intensity was slightly higher than the value of 100 mW/cm^2. The continuous-wave Doppler mode is very useful to record the maximal velocity along the Doppler beam, and the scanning time is very brief. In order to prevent an unnecessary Doppler exposure to the fetus, the scanning time of Doppler recordings was limited to 2 minutes, and the gain control was reduced to the minimum necessary to record adequate blood flow velocity waveform in our study. Moreover, all fetuses were subsequently delivered at Shimane Medical University Hospital without apparent fetal abnormalities.

Toshiyuki Hata, MD
Izumo, Japan
21 May 1987

DOPPLER PREDICTION OF TRANSVALVULAR GRADIENT AND STENOTIC ORIFICE AREA

Requarth et al[1] have studied the theoretical relation between pressure and flow, and used an in vitro model to verify a formula for valve area determination. This formula is based on the Gorlin equation[2] but applied to flow velocity measurements using ultrasound Doppler.[3] Unfortunately, they came up with some results, and especially interpretations, that are questionable and may create confusion regarding the hydraulic conditions at a stenotic valve. Their article has been quoted by others, and we feel that a clarification is necessary. It is partly possible to clarify some dubious interpretations of results, because the original data were fortunately published in the article. Because, however, quite some time has passed since this article was published, we will first summarize their model and the conclusions drawn from it. We will then comment on questionable results and present an alternative interpretation of some of their data.

To represent the flow situation at a stenotic valve, Requarth et al constructed a model where interchangeable orifices separated 2 tubes between which fluid streamed. The pressure p_1 was measured upstream to the orifice and p_2 immediately downstream. The fluid velocity through the orifice was obtained in 3 different ways: (1) velocity at the presumed vena contracta measured with pulsed ultrasound Doppler, (2) velocity ob-

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tained from measured volume flow measured orifice area assuming a value of 0.62 for the discharge coefficient and (3) velocity at vena contracta calculated from the simplified Bernoulli relation. Two areas were used: a true measured area and an area calculated from measured volume flow and ultrasound Doppler velocity assuming a discharge coefficient of 0.62. The 2 areas are compared.

We would like to comment on a misinterpretation in their Figure 2. It is apparent from the theory presented by Requarth et al that there is a square root relation between pressure gradient and flow. However, in the figure straight lines are fitted to the data points, which could indicate that they expected a linear relation. A major problem in their paper is the conclusions drawn from their data regarding the size of the discharge coefficient and the accuracy of the orifice area calculations. In their calculations of the area they used a theoretical value of 0.62 for the discharge coefficient. This theoretical value is a value for ideally sharp-edged orifices and may not be appropriate in this experimental situation.[4] For a specific orifice arrangement the real discharge coefficient has to be determined empirically. The data presented allows us to calculate real discharge coefficients as

$$C_d = Q/A_{true}\ vel_p$$

where Q is the measured volume flow and A_{true} the actual area of the orifice and vel_p the velocity at vena contracta calculated from the simplified Bernoulli relation. Our calculations give mean values of the discharge coefficient of 0.72, 0.77 and 0.85 for orifices with diameters of 10.4, 8.5 and 6.1 mm, respectively. Compared with other reported experimental data, we notice that the values 0.77 and 0.83 are high for this type of orifice. The reason for these discrepancies cannot fully be explained from the data presented and measurement errors cannot be excluded. Requarth et al do not discuss how the results are influenced by the fact that the flow velocity proximal to the hole is ignored and do not comment on errors of pressure measurements due to the location of the pressure tap.

Requarth et al found, using the discharge coefficient 0.62, that the calculated area was larger than the true area for the tested holes. For the smallest hole this overestimation was 27 to 40%. If one instead calculates the area using the measured discharge coefficient and the velocity measured by ultrasound Doppler, the calculated area will be in the range of −19% to +7% of the true area.

In the discussion section of this article, the deviations between actual and predicted orifice area at high flow rates through the smallest orifice were explained by limitations of the theoretical model. They claim that the real discharge coefficient might be larger than unity due to the spray effect distal to the orifice. The discharge coefficient, however, can by definition never be larger than unity, because that would violate basic physical principles like the first law of thermodynamics.

The too high orifice areas calculated by Requarth et al can definitely not be explained by a discharge coefficient larger than unity. The area of a fluid jet spray is associated with phenomena that cannot be described with a discharge coefficient concept. The explanation to the Requarth et al results lies in the use of a discharge coefficient deviating from the true one and in limitations of their experimental model.

Dan Loyd
Per Ask
Bengt Wranne
Linköping, Sweden
9 June 1987

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DECREASED HEART RATE VARIABILITY AND BETA BLOCKERS AFTER ACUTE MYOCARDIAL INFARCTION

Kleiger et al[1] recently reported the results of a large multicenter study. The major finding was that decreased heart rate (HR) variability—a predominant feature of impaired parasympathetic nervous function—assessed from Holter tapes was associated with an increased mortality after acute myocardial infarction (AMI). This finding is in accordance with previous reports on HR variability and HR and its association with mortality.[2,3] Experimental studies have also shown that dogs with a healed myocardial infarction and reduced levels of cardiac vagal activity are prone to exercise-induced ventricular fibrillation and subsequent increases in vagal activity protect against it.[4]

According to their Table VI the effect of blunted HR variability on mortality was partially neutralized by β-blocker treatment. The mortality of patients with decreased HR variability (<50 ms) was 37% compared with 8% in patients with normal HR variability (>100 ms) in the patient group not using β blockers. In the β blocker group the corresponding figures were 26% and 13%. This preliminary finding is in agreement with a previous report which showed that the favorable prognostic effect of β blocker treatment after AMI is related to the achieved HR reduction.[5] Heart rate is namely inversely related to HR variability.[1]

The association of diminished HR variability with the effectiveness of β blockade may be explained by the fact that the parasympathetic nervous system interacts with the sympathetic nervous system and can buffer the deleterious effects of a sympathetic storm on ventricular fibrillation threshold.[6] Thus, intact vagal function may protect the heart as does β blockade. On the basis of simple bedside tests impairment of parasympathetic nervous function is, however, common in coronary artery disease.[7]

The selection of patients who will probably benefit from long-term β-blocker treatment after AMI is an everyday problem. These findings of Kleiger et al suggest that assessing the vagal activity from Holter records or using simple bedside tests might give additional information in this decision-making.

K.E. Juhani Airaksinen, MD
Markku J. Ikäheimo, MD
Juha T. Takkunen, MD
Oulu, Finland
1 September 1987

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CARDIAC RHYTHM IN ATRIAL ISOMERISM

Although Wren and colleagues make a solid contribution to understanding the clinical expression of atrial isomerism,[1] there is a conceptual flaw in their definition of sinus rhythm: "Sinus rhythm was recorded if the PR interval was normal regardless of the P-wave axis." This is a curious definition of sinus rhythm, since the PR interval is created virtually entirely by the delay in the atrioventricular node.[2] Indeed, the P-wave axis was superior in 49% of patients with left isomerism. At least the −30° to −90° range was loosely known as "coronary sinus rhythm" based on Katz's criteria; as in their patients the leftward orientation of the pacemaker was frequently transient.[3] Moreover, Massumi and colleagues have shown that P-wave polarity was not a reliable guide to the site of the pacemaker.[4] Perhaps the authors chose to define sinus rhythm by the PR interval because in left atrial isomerism the sinus node is hypoplastic or absent and may be situated on the lateral wall of the atrium.[1]

David H. Spodick, MD, DSc
Worcester, Massachusetts
19 June 1987

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LONG-TERM FOLLOW-UP OF VALVULAR FUNCTION AFTER ORTHOTOPIC CARDIAC TRANSPLANTATION

In the June 1987 issue of the *Journal*, Lewen et al[1] describe the occurrence of tricuspid regurgitation (TR) after orthotopic heart transplantation, and suggest it to be an original observation. In fact, before Lewen's work had been submitted for publication to the *Journal* (January 5, 1986), this finding, and its relation to pulmonary hypertension, was published elsewhere,[2] and an article from our laboratory appeared in a November 1986 issue describing that valve regurgitation after heart transplantation involved the 4 cardiac valves and was transient in most patients.[3] Long-term follow-up of these patients indicates that tricuspid, mitral, aortic and pulmonary regurgitation suffers a gradual reduction in both their prevalence and importance (Table I).

The mechanism of such regurgitation can be ascribed to valve edema, and myocardial edema could also contribute[3]; certainly pulmonary hypertension contributes to both the presence and degree of TR.

One year after heart transplantation valve function is normal in most patients. Mild TR seen 1 year after the operation cannot be ascribed to a tricuspid valve abnormality as it is frequently observed in normal individuals.

Mercè Cladellas
Luisa Abadal
Manuel Ballester
Damià Obrador
Francesc Carreras
Guillem Pons-Lladó
Barcelona, Spain
4 September 1987

TABLE I Prevalence and Importance of Multivalvular Regurgitation After Orthotopic Cardiac Transplantation (20 Patients Followed for 1 Year)

Regurgitant Valve	Early (1 Week) Prevalence (%)	Late (1 Year) Prevalence (%)
Tricuspid	100*	95
Mild	55	100
Moderate	35	0
Severe	10	0
Mitral	75*	6
Mild	53	100
Moderate	47	0
Aortic	40	6
Pulmonary	25	0

HT = heart transplantation.
* Pulsed Doppler estimation of severity as described.[4,5]

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CORRECT NOMENCLATURE FOR THE CARDIOMYOPATHIES

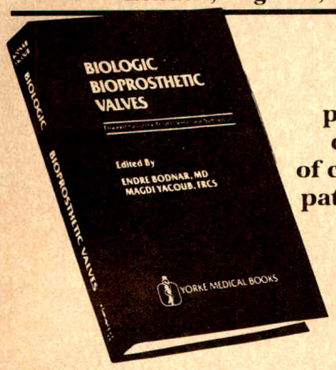
In his "From the editor" column Dr. Roberts is brief and succinct. One can agree or disagree with his statements—it is all put very clearly. In contrast to this it is rather irritating and frustrating that some Americans cannot or will not stick to the rules of nomenclature of cardiomyopathy. The topic ends up smothered—not debated. In 1980 the WHO Task Force Group on the Definition and Classification of Cardiomyopathy[1] (a group including a prominent American cardiologist) defined what was to be called cardiomyopathy, and what was to be called specific heart muscle disease. There is *no* such entity as ischemic cardiomyopathy although Americans continue to use this terminology (the latest example I have seen is Eisenberg et al[2]). I don't think I am a fusspot and my point is definitely not to discuss whether or not the definition of cardiomyopathy is an appropriate one. Simply put, my point is if you are playing (American) football the rules of soccer or baseball will not do. One has to stick to the rules until new and better ones have been decided upon. Emphasizing the American angle may be a little unfair as other nationalities are known to have broken the rules in the past, too. But it counts heavily when Americans are as influential in cardiology as they are in this case.

Ulrik Baandrup, MD
Aarhus, Denmark
25 September 1987

1. Report of the WHO/ISCF task force on the definition and classification of cardiomyopathies. *Br Heart J 1980;44:672-673.*
2. Eisenberg JD, Sobel BE, Geltman EM. *Differentiation of ischemic from nonischemic cardiomyopathy with positron emission tomography. Am J Cardiol 1987;59:1410–1414.*

Biologic & Bioprosthetic Valves

Proceedings of the Third International Symposium London, England, May 21-23, 1985



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The Third International Symposium on Cardiac Bioprostheses was held May 21-23, 1985, at the Grosvenor House Hotel, London. Six years have passed since the first meeting of this kind was held in Munich and 3 years since the second conference in Rome. The reassessment of the state of the art with biologic and bioprosthetic valves seems to have become a regular 3-yearly fixture reflecting the fast development of these devices, as well as the desire of surgeons and academics working in this field to share experiences, exchange ideas, and to resolve problems together.

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The Editors are eminently qualified to do this book, Dr. Bodnar is with the Cardiothoracic Institute, London, England, and Mr. Yacoub is with Harefield Hospital, Middlesex, England.

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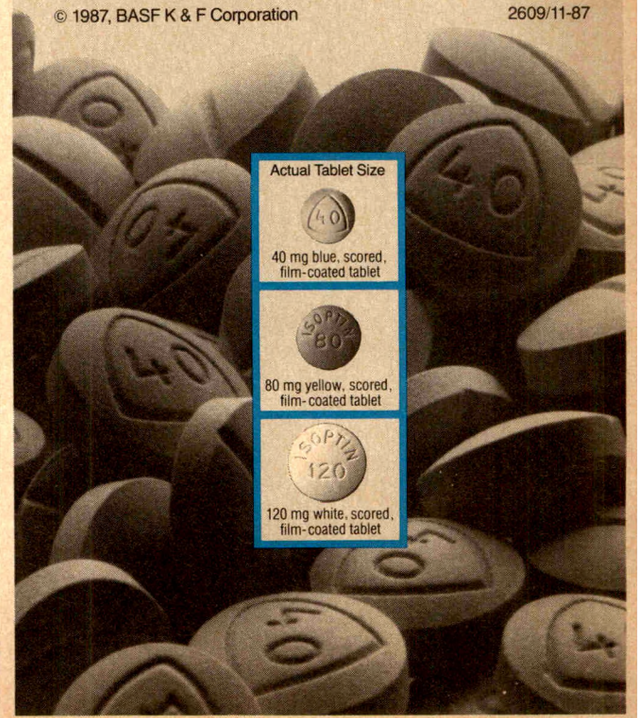

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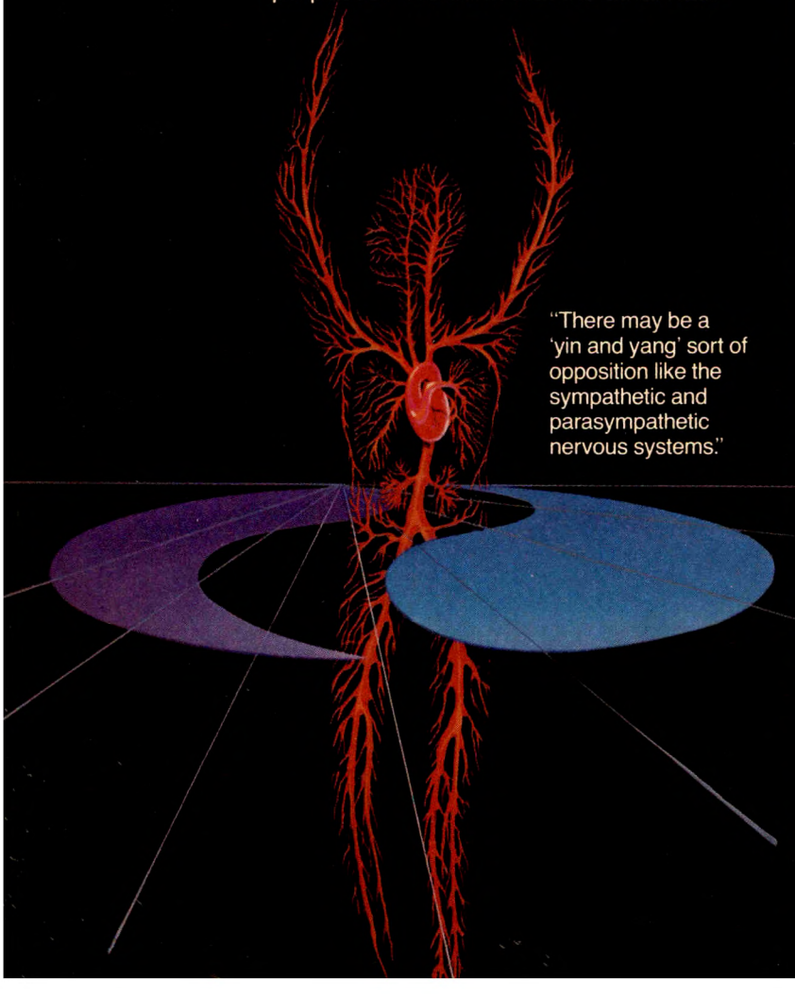

"There may be a 'yin and yang' sort of opposition like the sympathetic and parasympathetic nervous systems."

"Several years ago I suggested that the atrial peptide and RAA systems might be functional antagonists."
"And you can cite a number of areas where they are. Angiotensin constricts blood vessels; atrial peptides relax them. Angiotensin stimulates aldosterone production; atrial peptides inhibit it. The RAA system causes sodium retention—the atrial peptides cause natriuresis. And the atrial peptides inhibit renin release.

"Both angiotensin and atrial peptides are also present in the CNS, but it's not clear what they do. We have put atrial peptides into the CNS and shown they inhibit vasopressin release. Angiotensin appears to stimulate thirst, while atrial peptides antagonize angiotensin-induced water intake. There may be a 'yin yang' sort of opposition like the sympathetic and parasympathetic nervous systems."

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"If we can understand the natural physiologic controls, we may be able to alter them without stimulating counterregulatory mechanisms as occurs with diuretics and vasodilators. What we want to do is change the natural drives on the cardiovascular system so that the entire system readjusts back to a normal control point."

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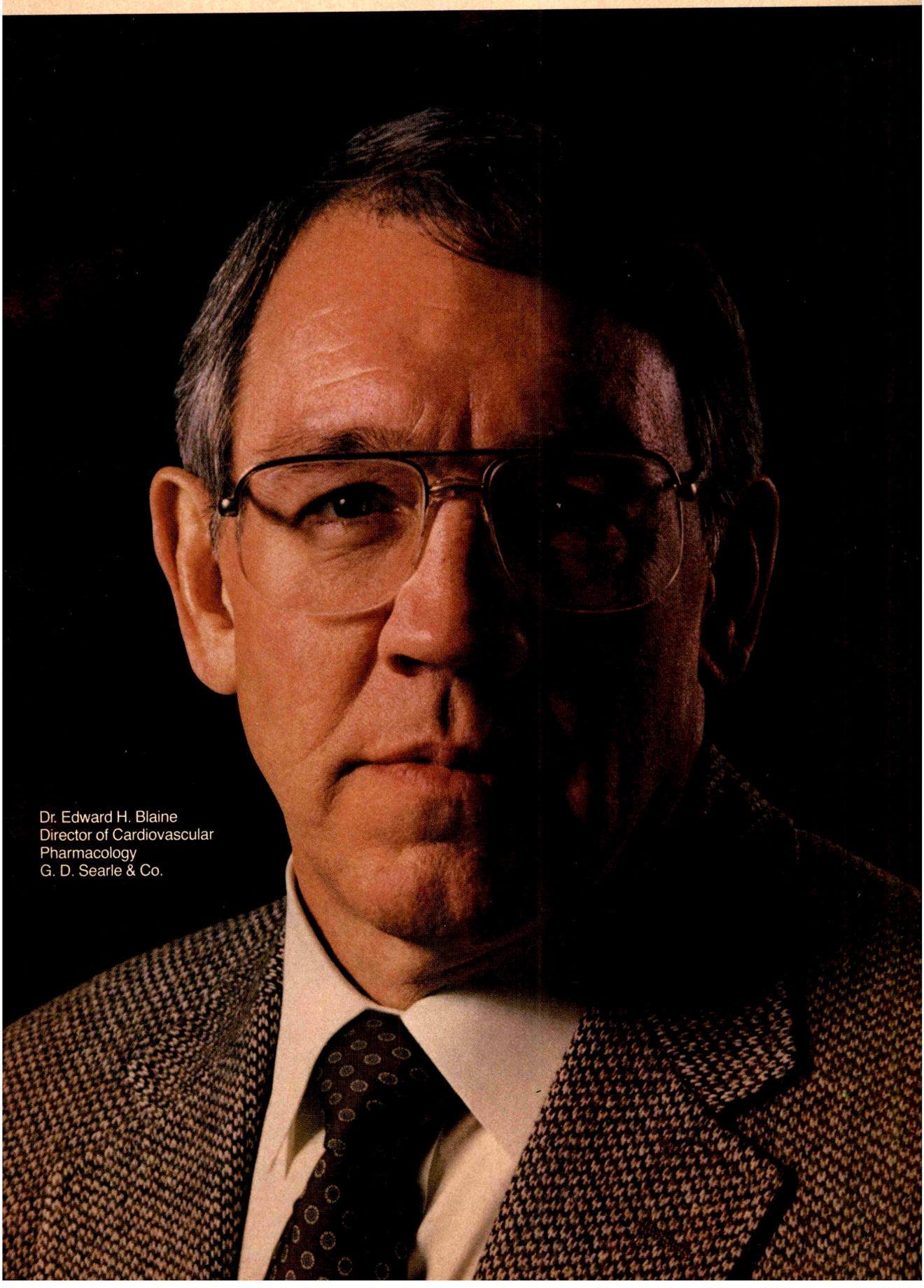

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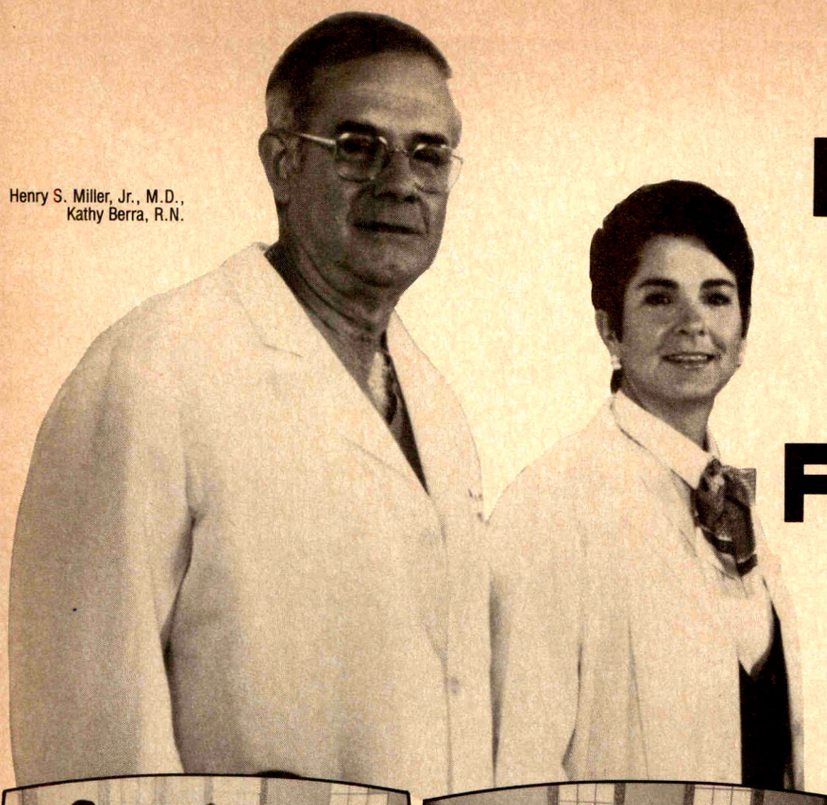

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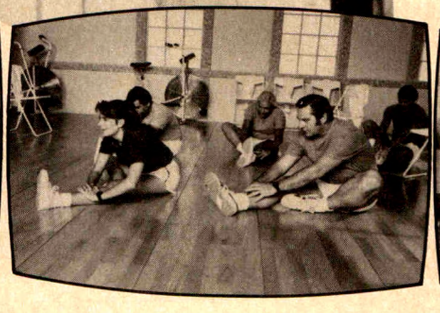

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Tambocor has a low incidence of cardiac side effects in patients with symptomatic PVCs and NSVT. In a study of 1,330 patients treated with Tambocor, the overall incidence of proarrhythmia was 6.8%. In patients with PVCs, the incidence was 1.7% (8/470); in NSVT patients, 3.8% (18/469).[4] However, Tambocor should be used with caution and dosed differently in patients with sustained V-tach, particularly those with congestive heart failure or myocardial dysfunction. The incidence of cardiac adverse effects has been found to be substantially higher in these patients. Please see full prescribing information.

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CONTRAINDICATIONS:
TAMBOCOR is contraindicated in patients with preexisting second- or third-degree AV block, or with right bundle branch block when associated with a left hemiblock (bifascicular block), unless a pacemaker is present to sustain the cardiac rhythm should complete heart block occur. TAMBOCOR is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARNINGS:
Proarrhythmic Effects. TAMBOCOR, like other antiarrhythmic agents, can cause new or worsened arrhythmias. Such proarrhythmic effects range from an increase in frequency of PVCs to the development of more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. In studies of TAMBOCOR, three fourths of proarrhythmic events were new or worsened ventricular tachyarrhythmias, the remainder being increased frequency of PVCs or new supraventricular arrhythmias. In patients with complex arrhythmias, it is often difficult to distinguish a spontaneous variation in the patient's underlying rhythm disorder from drug-induced worsening, so that the following occurrence rates must be considered approximations. Proarrhythmic effects were reported in 7% of patients treated with TAMBOCOR. Their frequency appears to be related to dose and to the underlying cardiac disease.
Among patients treated for sustained ventricular tachycardia (who frequently also had heart failure, a low ejection fraction, a history of myocardial infarction and/or an episode of cardiac arrest), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. In early studies in patients with sustained ventricular tachycardia utilizing a higher initial dose (400 mg/day) the incidence of proarrhythmic events was 26%; moreover, in about 10% of the patients treated proarrhythmic events resulted in death, despite prompt medical attention. With lower initial doses, the incidence of proarrhythmic events resulting in death decreased to 0.5% of these patients. Accordingly, it is extremely important to follow the recommended dosage schedule (see Dosage and Administration).
Patients with less serious arrhythmias (chronic PVCs and nonsustained ventricular tachycardia) have experienced a lower rate of proarrhythmic events, about 3%, with 0.1% being fatal.
The relatively high frequency of proarrhythmic events in patients with sustained ventricular tachycardia and serious underlying heart disease, and the need for careful titration and monitoring, requires that therapy of patients with sustained ventricular tachycardia be started in the hospital. Hospitalization should also be considered for other patients with underlying structural heart disease (see Dosage and Administration).
Heart Failure. TAMBOCOR has a negative inotropic effect and may cause or worsen congestive heart failure (CHF), particularly in patients with cardiomyopathy, preexisting severe heart failure (NYHA functional class III or IV) or low ejection fractions (less than 30%). New or worsened CHF which might be attributed to TAMBOCOR therapy occurred in approximately 5% of patients studied in various trials. CHF developed rarely (1%) in patients who had no previous history of CHF. Exacerbation of preexisting CHF occurred more commonly in studies which included patients with class III or IV failure than in studies which excluded such patients. TAMBOCOR should be used cautiously in patients who are known to have a history of congestive heart failure or myocardial dysfunction. The initial dosage in such patients should be no more than 100 mg bid (see Dosage and Administration) and patients should be monitored carefully. Close attention must be given to maintenance of cardiac function, including optimization of digitalis, diuretic, or other therapy. In cases where CHF has developed or worsened during treatment with TAMBOCOR, the time of onset has ranged from a few hours to several months after starting therapy. Some patients who develop evidence of reduced myocardial function while on TAMBOCOR can continue on TAMBOCOR with adjustment of digitalis or diuretics, others may require dosage reduction or discontinuation of TAMBOCOR. When feasible, it is recommended that plasma flecainide levels be monitored. Attempts should be made to keep trough plasma levels below 0.7 to 1.0 μg/ml.
Effects on Cardiac Conduction. TAMBOCOR slows cardiac conduction in most patients to produce dose-related increases in PR, QRS, and QT intervals.
The PR interval increases on average about 25% (0.04 seconds) and as much as 118% in some patients. Approximately one third of patients may develop new first degree AV heart block (PR interval ≥0.20 seconds). The QRS complex increases on average about 25% (0.02 seconds) and as much as 150% in some patients. Many patients develop QRS complexes with a duration of 0.12 seconds or more. In the study, 4% of patients developed new bundle branch block while on TAMBOCOR. The degree of lengthening of PR and QRS intervals does not predict either efficacy or the development of cardiac adverse effects. In clinical trials, it was unusual for PR intervals to increase to 0.30 seconds or more, or for QRS intervals to increase to 0.18 seconds or more. Thus, caution should be used when such intervals occur, and dose reductions may be considered. The QT interval widens about 8%, but most of this widening (about 60% to 90%) is due to widening of the QRS duration. The JT interval (QT minus QRS) only widens about 4% on the average. Significant JT prolongation occurs in less than 2% of patients. There has been one case of Torsade de Pointes-type arrhythmia associated with TAMBOCOR induced QT prolongation and bradycardia.
Clinically significant conduction changes have been observed at these rates: sinus node dysfunction such as sinus pause, sinus arrest and symptomatic bradycardia (1.2%), second-degree AV block (0.5%) and third-degree AV block (0.4%). An attempt should be made to manage the patient on the lowest effective dose in an effort to minimize these effects (see Dosage and Administration). If second- or third-degree AV block, or right bundle branch block associated with a left hemiblock occurs, TAMBOCOR therapy should be discontinued unless a temporary or implanted ventricular pacemaker is in place to ensure an adequate ventricular rate.
Sick Sinus Syndrome (Bradycardia-Tachycardia Syndrome). TAMBOCOR should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.
Effects on Pacemaker Thresholds. TAMBOCOR is known to increase endocardial pacing thresholds and may suppress ventricular escape rhythms. These effects are reversible if flecainide is discontinued. It should be used with caution in patients with permanent pacemakers or temporary pacing electrodes and should not be administered to patients with existing poor thresholds or nonprogrammable pacemakers unless suitable pacing rescue is available.
The pacing threshold in patients with pacemakers should be determined prior to instituting therapy with TAMBOCOR, again after one week of administration and at regular intervals thereafter. Generally threshold changes are within the range of multiprogrammable pacemakers and, when these occur, a doubling of either voltage or pulse width is usually sufficient to regain capture.
Electrolyte Disturbances. Hypokalemia or hyperkalemia may alter the effects of class I antiarrhythmic drugs. Preexisting hypokalemia or hyperkalemia should be corrected before administration of TAMBOCOR.

PRECAUTIONS:
Drug Interactions. TAMBOCOR has been administered to patients receiving digitalis preparations or beta-adrenergic blocking agents without adverse effects. During administration of multiple oral doses of TAMBOCOR to healthy subjects stabilized on a maintenance dose of digoxin, a 13% ± 19% increase in plasma digoxin levels occurred at six hours postdose.
In a study involving healthy subjects receiving TAMBOCOR and propranolol concurrently, plasma flecainide levels were increased about 20% and propranolol levels were increased about 30% compared to control values. In this formal interaction study, TAMBOCOR and propranolol were each found to have negative inotropic effects; when the drugs were administered together, the effects were additive. The effects of concomitant administration of TAMBOCOR and propranolol on the PR interval were less than additive. In TAMBOCOR clinical trials, patients who were receiving beta blockers concurrently did not experience an increased incidence of side effects. Nevertheless, the possibility of additive negative inotropic effects of beta blockers and flecainide should be recognized.
Flecainide is not extensively bound to plasma proteins. In vitro studies with several drugs which may be administered concomitantly showed that the extent of flecainide binding to human plasma proteins is either unchanged or only slightly less. Consequently, interactions with other drugs which are highly protein bound (e.g., anticoagulants) would not be expected. TAMBOCOR has been used in a large number of patients receiving diuretics without apparent interaction. Limited data in patients receiving known enzyme inducers (phenytoin, phenobarbital, carbamazepine) indicate only a 30% increase in the rate of flecainide elimination. In healthy subjects receiving cimetidine (1 gm daily) for one week, plasma flecainide levels increased by about 30% and half-life increased by about 10%.
When amiodarone is added to flecainide therapy, plasma flecainide levels may increase two-fold or more in some patients, if flecainide dosage is not reduced. (See Dosage and Administration.)
There has been little experience with the coadministration of TAMBOCOR and either disopyramide or verapamil. Because both of these drugs have negative inotropic properties and the effects of coadministration with TAMBOCOR are unknown, neither disopyramide nor verapamil should be administered concurrently with TAMBOCOR unless, in the judgement of the physician, the benefits of this combination outweigh the risks. There has been too little experience with the coadministration of TAMBOCOR with nifedipine or diltiazem to recommend concomitant use.
Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies with flecainide in rats and mice at doses up to about eight times the usual human dose of 8 mg/kg/day (assuming patient weight of 50 kg) have not revealed any compound-related carcinogenic effects. Mutagenicity studies (Ames test, mouse lymphoma and in vivo cytogenetics) did not reveal any mutagenic effects. A rat reproduction study at doses up to 50 mg/kg/day (seven times the usual human dose) did not reveal any adverse effect on male or female fertility.
Pregnancy. Pregnancy Category C. Flecainide has been shown to have teratogenic effects (club paws, sternebrae and vertebrae abnormalities, pale hearts with contracted ventricular septum) and an embryotoxic effect (increased resorptions) in one breed of rabbit (New Zealand White) but not in another breed of rabbit (Dutch Belted) when given in doses about four times (but not three times) the usual human dose (assuming a patient weight of 50 kg). No teratogenic effects were observed in rats and mice given doses up to 50 and 80 mg/kg/day, respectively; however, delayed sternebral and vertebral ossification was observed at the high dose in rats. Because there are no adequate and well-controlled studies in pregnant women, TAMBOCOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery. It is not known whether the use of TAMBOCOR during labor or delivery has immediate or delayed adverse effects on the mother or fetus, affects the duration of labor or delivery, or increases the possibility of forceps delivery or other obstetrical intervention.
Nursing Mothers. Limited data suggest that flecainide is excreted in human milk. Because of the drug's potential for serious adverse effects in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use. The safety and effectiveness of TAMBOCOR in children less than 18 years of age have not been established.
Hepatic Impairment. Since flecainide elimination from plasma can be markedly slower in patients with significant hepatic impairment, TAMBOCOR should not be used in such patients unless the potential benefits clearly outweigh the risks. If used, frequent and early plasma level monitoring is required to guide dosage (See Plasma Level Monitoring); dosage increases should be made very cautiously when plasma levels have plateaued (after more than four days).

ADVERSE EFFECTS:
The most serious adverse effects reported for TAMBOCOR, described in detail in Warnings section, were new or exacerbated ventricular arrhythmias which occurred in 7% of patients, and new or worsened congestive heart failure which occurred in approximately 5% of patients. In some patients, TAMBOCOR treatment has been associated with episodes of unresuscitatable ventricular tachycardia or ventricular fibrillation. There have also been instances of second- (0.5%) or third-degree (0.4%) AV block. Patients have developed sinus bradycardia, sinus pause, or sinus arrest, about 1.2% altogether (see Warnings). The frequency of most of these serious adverse events probably increases with higher trough plasma levels, especially when these trough levels exceed 1.0 μg/ml.
There have been rare reports of isolated elevations of serum alkaline phosphatase and isolated elevations of serum transaminase levels. These elevations have been asymptomatic and no cause and effect relationship with TAMBOCOR has been established. In foreign postmarketing surveillance studies, there have been rare reports of hepatic dysfunction including reports of cholestasis and hepatic failure, and extremely rare reports of blood dyscrasias. Although no cause and effect relationship has been established, it is advisable to discontinue TAMBOCOR in patients who develop unexplained jaundice or signs of hepatic dysfunction or blood dyscrasias in order to eliminate TAMBOCOR as the possible causative agent.
Incidence figures for other adverse effects are based on a multicenter efficacy study, utilizing starting doses of 200 mg/day with gradual upward titration to 400 mg/day. Patients were treated for an average of 4.7 months, with some receiving up to 22 months of therapy. In this trial, 5.4% of patients discontinued due to non-cardiac adverse effects.

Table 1
Most Common Adverse Effects in Patients Treated With TAMBOCOR in the Multicenter Study

Adverse Effect	Incidence in All 429 Patients at Any Dose	Incidence by Dose During Upward Titration: 200 mg/Day (N=426)	300 mg/Day (N=293)	400 mg/Day (N=100)
Dizziness*	18.9%	11.0%	10.6%	13.0%
Visual Disturbance†	15.9%	5.4%	12.3%	18.0%
Dyspnea	10.3%	5.2%	7.5%	4.0%
Headache	9.6%	4.5%	6.1%	9.0%
Nausea	8.9%	4.9%	4.8%	6.0%
Fatigue	7.7%	4.5%	4.4%	3.0%
Palpitation	6.1%	3.5%	2.4%	7.0%
Chest Pain	5.4%	3.1%	3.8%	1.0%
Asthenia	4.9%	2.6%	2.0%	4.0%
Tremor	4.7%	2.4%	3.4%	2.0%
Constipation	4.4%	2.8%	2.1%	1.0%
Edema	3.5%	1.9%	1.4%	2.0%
Abdominal Pain	3.3%	1.9%	2.4%	1.0%

*Dizziness includes reports of dizziness, lightheadedness, faintness, unsteadiness, near syncope, etc.
†Visual disturbance includes reports of blurred vision, difficulty in focusing, spots before eyes, etc.

In a trial in ambulatory patients with frequent premature ventricular complexes and nonsustained ventricular tachycardia utilizing a starting dose of 400 mg/day and a maintenance dose of 400-600 mg/day, the incidence of these adverse experiences was similar, except for dizziness (32%) and visual disturbances (28%).
The following additional adverse experiences, possibly related to TAMBOCOR therapy and occurring in 1% to less than 3% of patients, have been reported in acute and chronic studies: *Body as a Whole*—malaise, fever; *Cardiovascular*—tachycardia, sinus pause or arrest; *Gastrointestinal*—vomiting, diarrhea, dyspepsia, anorexia; *Skin*—rash; *Visual*—diplopia; *Nervous System*—hypoesthesia, paresthesia, paresis, ataxia, flushing, increased sweating, vertigo, syncope, somnolence, tinnitus; *Psychiatric*—anxiety, insomnia, depression.
The following additional adverse experiences, possibly related to TAMBOCOR, have been reported in less than 1% of patients: *Body as a Whole*—Swollen lips, tongue and mouth; arthralgia, bronchospasm, myalgia; *Cardiovascular*—angina pectoris, second-degree and third-degree AV block, bradycardia, hypertension, hypotension; *Gastrointestinal*—flatulence; *Urinary System*—polyuria, urinary retention; *Hematologic*—leukopenia, thrombocytopenia; *Skin*—urticaria, exfoliative dermatitis, pruritus; *Visual*—eye pain or irritation, photophobia, nystagmus; *Nervous System*—twitching, weakness, change in taste, dry mouth, convulsions, impotence, speech disorder, stupor; *Psychiatric*— amnesia, confusion, decreased libido, depersonalization, euphoria, morbid dreams, apathy.

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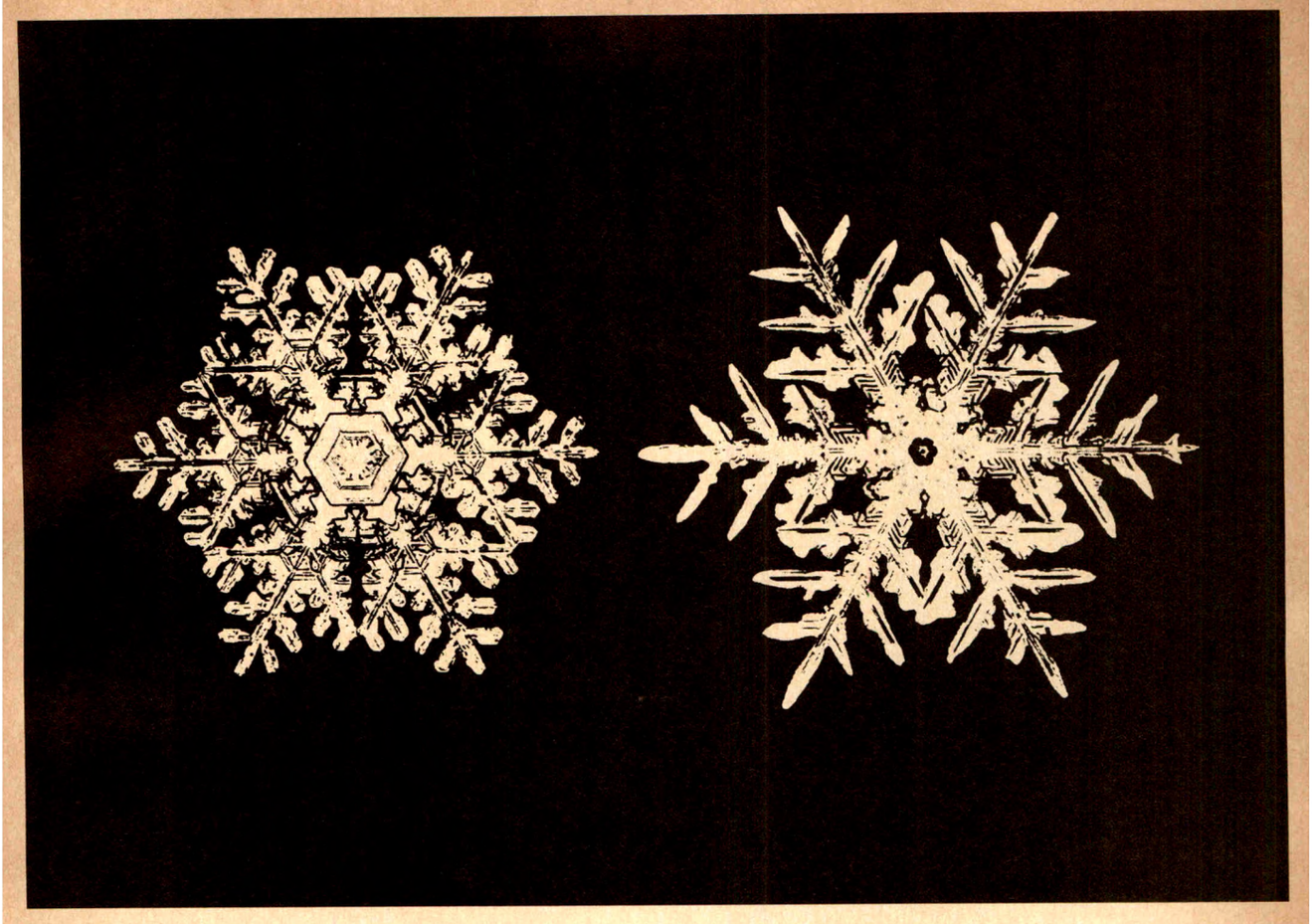

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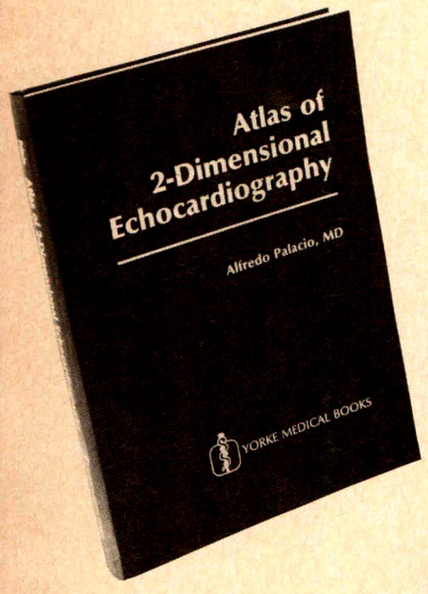

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efore prescribing, please see full prescribing information.
Brief Summary follows.

The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

IDICATIONS AND USAGE: Oral procainamide is indicated in the treatment of premature entricular contractions, ventricular tachycardia, atrial fibrillation, and paroxysmal atrial achycardia.

ONTRAINDICATIONS: Hypersensitivity to procainamide is an absolute contraindication. In this onnection, cross-sensitivity to procaine and related drugs must be borne in mind.

Procainamide should not be administered to patients with complete atrioventricular heart block. is also contraindicated in cases of second degree and third degree A-V nodal block unless an lectrical pacemaker is operative.

It has been suggested that procainamide be contraindicated in patients with myasthenia gravis.

ARNINGS: Granulocytopenia may follow the use of procainamide, and deaths from sepsis have ccurred. Leukocyte changes are most likely to occur during the first three months of therapy. During this time routine blood counts should be done at least every two weeks and thereafter at onger intervals throughout maintenance procainamide therapy. Complaints of malaise and aches a flu-type syndrome) are often reported in association with the granulocyte depression.

Patients should be instructed to report such symptoms promptly, as well as any soreness of nouth, throat or gums, unexplained fever, or symptoms of an upper respiratory tract infection. If hese should occur and a complete blood count indicates a granulocyte depression, procainamide herapy should be discontinued immediately and appropriate treatment instituted. Recovery of eukocyte count usually occurs within a few weeks.

The incidence of granulocytopenia appears to be higher with procainamide sustained-release ablets than with standard tablets.

RECAUTIONS: General — During administration of the drug, evidence of untoward myocardial esponses should be carefully watched for in all patients. In the presence of an abnormal nyocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, he ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization educes, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole s particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgment of mural thrombi and produce an embolic episode. However, it has been suggested that, in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient reevaluated since asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney disease, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Serious hypotension can result from peripheral vasodilation and from decreases in cardiac output. At high plasma levels, procainamide may produce sinus tachycardia due to reflex sympathetic response to its hypotensive effect. Large doses may increase cardiac automaticity and can induce complete atrioventricular block, cardiac standstill, or ventricular extrasystoles that may proceed to ventricular fibrillation. These effects on the myocardium are reflected in the electrocardiogram: a widening of the QRS complex occurs most consistently; less regularly, the P-R and Q-T intervals are prolonged; and the QRS and T waves show some decrease in voltage.

Antinuclear antibodies (ANA) are often found in patients receiving long-term procainamide therapy. The induction of ANA appears to be independent of dosage. Patients with procainamide-induced increases in ANA titers may develop a syndrome resembling systemic lupus erythematosus (SLE). The mechanism of this syndrome is uncertain. Polyarthralgia, arthritic symptoms, and pleuritic pain are common symptoms; to a lesser extent fever, myalgia, skin lesions, pleural effusion, pericarditis, headache, fatigue, weakness, nausea and abdominal pain may occur. Rare cases of thrombocytopenia, Coombs' positive hemolytic anemia, increased SGOT, SGPT, and serum amylase have been reported which may be related to this SLE-like syndrome.

It is recommended that tests for systemic lupus erythematosus be carried out at regular intervals in patients receiving maintenance or prolonged procainamide therapy. The drug should be discontinued if there is a rising ANA titer or clinical symptoms of SLE appear. The SLE-like syndrome may be reversible upon discontinuation of the drug. If discontinuation does not cause remission of the symptoms, corticosteroid therapy may be effective. If the SLE-like syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, corticosteroid suppressive therapy may be used concomitantly with procainamide.

Information for Patient — Practitioners should give the following information and instructions to patients receiving Procan SR. 1. Do not crush or chew these tablets. Swallow them whole. 2. Take this medicine exactly as directed by your doctor. Do not miss any doses and do not take more medicine than ordered. Do not stop taking this medicine without first checking with your doctor. 3. If you miss a dose and remember within one hour or so, take it as soon as possible. Then go back to your regular dosing schedule. Do not take double doses. If you have any questions about this, check with your doctor. 4. Report to your doctor any flu-type symptoms, such as malaise and aches, as well as any soreness of the mouth, throat or gums, unexplained fever, skin rash, unusual bleeding or bruising, symptoms that resemble arthritis, or symptoms of an upper respiratory tract infection. 5. Do not be concerned if you occasionally notice in your stool something that looks like a tablet. In Procan SR (procainamide hydrochloride tablets), the drug is "held" in a wax core that has been specially designed to slowly release the drug for your body to absorb. When this process is completed the empty, nonabsorbable wax core, which looks nearly unchanged, is eliminated from your body. 6. Keep container tightly closed and store in a cool, dry place.

Procan® SR (procainamide hydrochloride tablets)

Laboratory Tests — Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals.

Routine blood counts are advisable during maintenance procainamide therapy. See WARNINGS for additional information.

Plasma concentrations of procainamide and NAPA should be monitored in patients with renal disease, hepatic disease, cardiac failure, or low cardiac output states.

Drug Interactions: 1. **Antiarrhythmics:** Concurrent use with procainamide may result in additive cardiac effects and/or additive toxic effects. 2. **Anticholinergics:** Procainamide enhances the anticholinergic effects. Extreme caution must be exercised with such a combination. 3. **Anticholinesterases:** Procainamide antagonizes the effect of anticholinesterases in myasthenia gravis, and paralysis returns. 4. **Antihypertensives:** Procainamide may potentiate the hypotensive effects of thiazide diuretics and other antihypertensive agents. Adjustment of dosage may be required. 5. **Histamine H_2-receptor antagonists:** It has been reported that histamine H_2-receptor antagonists such as cimetidine and ranitidine reduce renal clearance of procainamide and NAPA, resulting in higher plasma concentrations for longer durations. Caution should be exercised when administering these drugs concurrently, especially in the elderly, who have a reduced ability to clear all three. Dosage modification may be required. 6. **Neuromuscular Blocking Agents:** Procainamide potentiates the effects of skeletal muscle relaxants such as succinylcholine. It also may enhance or prolong the neuromuscular blocking activity of bacitracin, colistimethate, dihydrostreptomycin, gentamicin, gramicidin, kanamycin, neomycin, polymyxin B, streptomycin, and viomycin, producing respiratory depression.

Pregnancy — Pregnancy Category C. Animal reproduction studies have not been conducted with procainamide. It is also not known whether procainamide can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Procainamide should be given to a pregnant woman only if clearly needed.

Nursing Mothers — Procainamide and its major metabolite, NAPA, have been identified in breast milk. Caution should be exercised when procainamide is administered to a nursing woman.

ADVERSE REACTIONS: Most frequent, especially with large oral doses: 1. Anorexia; 2. Nausea; 3. Vomiting; 4. Diarrhea; 5. Urticaria; 6. Pruritus.

Less frequent: 1. Reactions in patients on long-term procainamide therapy: a. Antinuclear antibodies (ANA); b. Syndrome resembling systemic lupus erythematosus (SLE) (See PRECAUTIONS); 2. Hypersensitivity reactions: a. Angioneurotic edema; b. Maculopapular rash; c. Fever; d. Eosinophilia; e. Hypergammaglobulinemia.

Infrequent: 1. Granulocytopenia, sometimes resulting in death (See WARNINGS); 2. Convulsions; 3. Psychosis with hallucinations; 4. Confusion; 5. Mental depression; 6. Giddiness; 7. Lightheadedness; 8. Weakness; 9. Bitter taste.

Rare: 1. Hypotension; 2. A case was reported with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following a single dose of the drug.

OVERDOSAGE: Signs and Symptoms: Severe hypotension, ventricular fibrillation, widening of QRS complex, junctional tachycardia, intraventricular conduction delay, oliguria, lethargy, confusion, nausea, and vomiting.

Treatment: If ingestion is recent, emesis, activated charcoal, or gastric lavage may reduce absorption. Dopamine, phenylephrine, or levarterenol may be helpful in reversing severe hypotensive responses.

Management of overdosage includes symptomatic treatment with ECG and blood pressure monitoring. Procainamide toxicity can usually be treated, if necessary, by administering vasopressors after adequate fluid volume replacement. Intravenous infusion of 1/6 molar sodium lactate injection reportedly reduces the cardiotoxic effects of procainamide.

If procainamide toxicity causes severe hypotension and renal insufficiency, urinary elimination of procainamide and NAPA is decreased, and hemodialysis may be required. Hemodialysis significantly reduces the serum half-life of procainamide, and effectively removes procainamide and NAPA. Peritoneal dialysis is not effective.

It has been reported that one patient who ingested approximately 7 grams of procainamide hydrochloride recovered after treatment consisting of IV levarterenol, IV furosemide, attempted volume expansion with albumin, and hemodialysis. Also reported is the case of an elderly patient who recovered after ingestion of approximately 19 grams of procainamide hydrochloride. The patient was treated with IV isoproterenol and IV epinephrine. The latter report suggested that insertion of a ventricular pacing electrode is a reasonable precautionary measure in case high grade A-V block develops.

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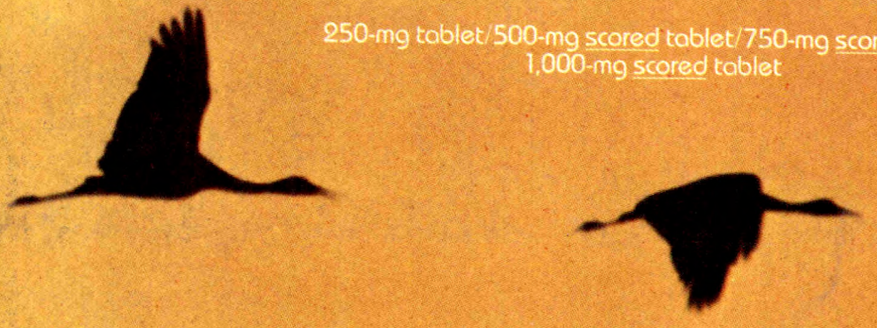

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A Symposium: Silent Myocardial Ischemia and Infarction— Past, Present and Future

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David P. Lauler, MD

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Editor:
David P. Lauler, MD
Clinical Associate Professor of Medicine
Yale University School of Medicine
New Haven, Connecticut
Chairman, Department of Medicine
Director of Medical Education
Lawrence and Memorial Hospitals
New London, Connecticut

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APRIL 21, 1988

The American Journal of CARDIOLOGY®

VOLUME 61

NUMBER 12

A Symposium: Silent Myocardial Ischemia and Infarction—Past, Present and Future

Introduction

DAVID P. LAULER, MD

To further our understanding of angina and silent myocardial ischemia, angina and infarction, members of the National Council on Silent Myocardial Ischemia & Infarction gathered to exchange the latest information on the prognosis and clinical management of patients with asymptomatic coronary disease. The meeting, held in Palm Beach, Florida, on September 11 to 12, 1987, was chaired and moderated by Dr. Peter F. Cohn. The presentations and discussions from this conference provide the source for this special issue of *The American Journal of Cardiology*.

The opening presentation by Dr. David Sheps focused on the abnormal pain perception documented in subsets of patients with silent myocardial ischemia. Results reported to date on endorphin/enkephalin measurements are discrepant, perhaps because different laboratory assay methods have been utilized in various types of patients.

A different perspective on silent myocardial ischemia was offered by Dr. Bimlendra Sharma from his analysis of the Hennepin County Medical Center study on out-of-hospital ventricular fibrillation. From 1974 to 1979, 1,070 patients were admitted to the emergency room of Hennepin County Hospital after an episode of out-of-hospital ventricular fibrillation. Of the 325 who were admitted to the coronary care unit, 150 survived. Among those selected for evaluation and long-term follow-up, 15 underwent preexercise and postexercise cardiac hemodynamic evaluation. There were no significant differences between patients in whom ventricular fibrillation was the initial manifestation of coronary disease and those previously known to have angina or infarction. Certain patients had a marked increase in left ventricular end-diastolic pressure without pain during exercise. Of the first 32 deaths that occurred during follow-up, 26 were sudden. Dr. Sharma's studies were interesting in that they provided objective electrocardiographic and hemodynamic evidence of exercise-induced, painless, myocardial ischemia.

Whereas these studies afforded a retrospective viewpoint of coronary artery disease, Dr. Lewis Becker gave a prospective analysis in his report of findings in asymptomatic siblings of patients with premature coronary artery disease. Because the material is being prepared for more detailed publication elsewhere, it is not included in this issue.

The significance of ST-segment depression recorded with Holter monitoring during daily activities was reported by Dr. Shlomo Stern in a study comparing patients with and without prior myocardial infarctions. These "ischemic" ST changes were associated with a higher rate of cardiac events in both groups, and reflected prognostic information, independent of stress tests, left ventricular ejection fraction or extent of coronary disease.

Dr. Stern's observation concerning the prognostic value of transient silent myocardial ischemia was reinforced during a presentation by Dr. Michael E. Assey, who, in his study of patients with documented coronary artery disease, found a significantly ($p = 0.05$) higher incidence (22%) of acute myocardial infarction in the subgroup with silent ischemia compared with that in the symptomatic group (4%). In this same study, the incidence of death was 11% in the group with

From the Yale University School of Medicine, New Haven, Connecticut.

silent myocardial ischemia compared with 0% in the group with angina.

Reports from Drs. Peter Cohn and Gary Gerstenblith addressed the prognostic significance of silent myocardial ischemia in asymptomatic patients and in those with unstable angina, respectively. A forthcoming publication elsewhere precludes their appearance in this supplement.

The rationale for the use of exercise radionuclide imaging for the detection of silent myocardial ischemia was presented by Dr. George A. Beller. His comments emphasized the greater sensitivity and specificity of this technique compared with exercise stress testing, and especially its ability to detect the onset of ischemia-induced perfusion abnormalities occurring before angina. Such perfusion abnormalities in post-MI patients identify a high-risk subset.

Dr. Mitchell Krucoff emphasized the quantitation of myocardial ischemia, using graphic projections of standard 12-lead electrocardiograms taken every 30 seconds and digital information storage. This permits viewing and analysis of data in 3 dimensions—ST levels, electrocardiographic lead and time—and also enables the calculation of a time-severity index for quantitating myocardial ischemic episodes. Dr. Krucoff and his associates noted that 78% of patients undergoing balloon angioplasty exhibited ST-segment deviations, which consisted of elevation in 67%. In the 19-hour period after angioplasty, 23% (65 patients) had ST deviation. Of this group, 38% had no symptoms, 22% had some symptoms, and 15% had a 15-minute or greater "silent" period before the onset of symptoms—a therapeutic window for aggressive intervention. Overall, 84% of patients after angioplasty had some evidence of silent myocardial ischemia.

The resurgence of interest in the entity of non-Q-wave infarction was evident during a presentation by Dr. Marcus A. DeWood, who reported that angiographically documented thrombus is found in 30 to 40% of patients with non-Q-wave infarction, and increases only slightly with time. The underlying mechanism for infarction in these patients may be platelet microaggregation or abnormal microvasomotion, or both.

Regarding therapy of patients with silent myocardial ischemia, Dr. Eliot Lazar presented Dr. William Frishman's data from a crossover trial that compared diltiazem with nifedipine in 20 patients with stable angina. Because it is to be published elsewhere, his presentation has been omitted.

This national meeting concluded with a focus on the "real-world" dilemmas of the practicing physician. Dr. John Schroeder presented selected cases from his own practice, which illustrated the role of exercise testing and ambulatory electrocardiographic evaluation in diagnosing silent myocardial ischemia in patients known or suspected to have coronary artery disease. Dr. Schroeder also included therapeutic considerations, ranging from the selective use of calcium channel blockers to consideration of coronary bypass surgery.

The bottom line for the practicing physician involves treatment of silent ischemia. Since a working definition of silent myocardial ischemia is readily grasped, i.e., ischemia in the absence of symptoms, physicians will probably be reformulating their therapeutic approach to such patients. Emphasis will be on totality of treatment, with "round-the-clock" coverage for both silent and nonsilent (angina or anginal equivalents) episodes. Because most episodes of silent myocardial ischemia occur during routine daily activities and at normal heart rates, suggesting that abnormal coronary vasomotion may be playing a role, greater use of the calcium-blocking agents can be anticipated. Which of the calcium blockers to specifically use will undoubtedly be determined by their overall adverse-effect profile, a particularly important feature when treating an asymptomatic disease.

Endorphins and Pain Perception in Silent Myocardial Ischemia

DAVID S. SHEPS, MD, ALAN HINDERLITER, MD, EDITH E. BRAGDON, MA, KIRKWOOD F. ADAMS, MD, MARGARET C. HERBST, RN, MSN, and GARY KOCH, PhD

Evidence suggests that endogenous opioids, particularly the β-endorphins and met-enkephalins, are closely involved in stress-induced analgesia and nociceptive pain control. Numerous investigations have been conducted to evaluate the role of opioids in silent vs symptomatic myocardial disease. There is good evidence to suggest that patients with asymptomatic ischemia have defective pain perception compared with those with angina; however, the precise role of the endorphin and enkephalin systems in this phenomenon remains to be elucidated. Possible sources for disparate study results include variation in patient populations, insensitive or improperly timed assay techniques, and differences in amount of ischemia.

(Am J Cardiol 1988;61:3F–6F)

The endogenous opioids are derived from larger precursor molecules. For example, pro-enkephalin A gives rise to several molecules of methionine (met)-enkephalin and 1 molecule of leucine-enkephalin. Dynorphin is created by cleavage of pro-dynorphin. Pro-opiomelanocortin is the progenitor of β-endorphin, the most potent endogenous opioid peptide yet discovered. Endogenous opioids are pharmacologically similar to, and show cross-tolerance with, morphine. Their action is reversed by naloxone.

Enkephalins, abundant throughout the central nervous system, are also found in the gut, sympathetic nervous system and adrenal medullary chromaffin cells. Dynorphin peptides are located similarly but are released from different cells; their function has not been clearly delineated. Beta-endorphins are produced in cells located in the arcuate nucleus of the hypothalamus and the pituitary. Each of these types of opioid peptides are contained in structures closely involved with nociceptive pain control.

From the Cardiology Division, University of North Carolina School of Medicine, Chapel Hill, North Carolina. This study was supported in part by the Cooperative Agreement CR807392 from the Environmental Protection Agency, Washington, D.C., and in part by Grant 1-R01-HL38168 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland.

Address for reprints: David S. Sheps, MD, Cardiology Division, University of North Carolina School of Medicine, 338 Clinical Sciences Building 229 H-CB #7075, Chapel Hill, North Carolina 27514.

Circulating endorphins are probably important in stress-induced analgesia. For instance, hypophysectomy or adrenomedullectomy in rats blunts opioid-dependent analgesia.[1,2] A recent study by Carr suggests that reflux of β-endorphins from blood into cerebrospinal fluid (CSF) contributes to an increase in CSF endorphin levels.[3] Endorphin levels are increased in response to exercise, in a magnitude that is directly related to the intensity of effort and degree of training. A case in point is the well-documented rise in plasma β-endorphin and met-enkephalin levels that occurs after running.

The evidence that psychological stressors influence circulating endorphin levels in humans is inconclusive. Reports have been published associating increased β-endorphin levels with the stress of an impending examination, and increased opioid activity has been observed in subjects engaged in cognitive and attentive tasks. In these studies, the amount of subjective stress experienced was closely related to opioid levels, suggesting a direct relation between endorphin response, psychophysiologic arousal and personality variables.[4]

Pain Perception in Patients with Asymptomatic Ischemia

The conflicting results of various investigations obscure the precise role of endorphins in the pathogenesis of silent myocardial ischemia.

In 1983, Droste and Roskamm[5] studied pain thresholds and tolerance in 20 patients with asymptomatic

TABLE I Summary of Studies Investigating the Effect of Naloxone on Pain Response in Patients with Myocardial Ischemia

	Droste & Roskamm 1984[5]	Ellestad & Kuan 1984[8]	Van Rijn & Rabkin 1986[7]
Subject	30 asymptomatic and 30 symptomatic on exercise testing	10 without angina; 7 = type I, 3 = type II (post–MI)	5 with exercise-induced angina
Type test	Cold pressor Electric skin stimulation Ischemic forearm tourniquet test Repeat testing after naloxone and placebo in 10 asymptomatics	2 multistage treadmill tests in 1 week, with naloxone injected before the 2nd test	3 multistage treadmill tests in 3 successive weeks: control; naloxone & placebo double-blind
Naloxone	2 mg before pain tests	2 mg before 2nd test	2 mg, 5 min before 2nd or 3rd test
Results	Threshold & tolerance levels slightly decreased after naloxone (forearm pain only)	No angina in any subject, with or without naloxone	Angina significantly earlier after naloxone, compared with placebo

MI = myocardial infarction.

ischemia and 22 patients with reproducible angina. All patients with silent myocardial ischemia had a higher threshold for electrical and forearm ischemic pain and a higher tolerance for cold pressor and forearm ischemic pain than those with some angina. The responses of the 42 subjects on the Freiberger Personality Inventory Test elicited different psychological profiles for the 2 groups, which the investigators believed might contribute to discrepant pain thresholds. In 1984, these same investigators used the same experimental measures to test pain response in 30 asymptomatic and 30 anginal patients with myocardial ischemia, and again found higher thresholds and tolerance levels for the aforementioned stressors in the asymptomatic group. To evaluate the role of endogenous opioids in this pain perception, 10 asymptomatic patients were given 2 mg of naloxone. Threshold and tolerance levels for forearm ischemic pain were significantly decreased and were no longer substantially different from those of angina patients. In fact, 2 of the 10 patients had chest pain after naloxone administration.[6] These results suggest—although they do not prove—that the lack of symptoms in patients with silent myocardial ischemia is due to a generalized hyposensitivity to pain, and that higher levels of pain tolerance might be mediated by endorphins.

Data concerning the effects of opioid antagonists on the perception of myocardial ischemia are conflicting (Table I). Van Rijn and Rabkin[7] reported that administration of 2 mg of naloxone resulted in the earlier appearance of chest pain during treadmill testing in 6 patients with exercise-induced angina. Ellestad and Kuan[8] and Cohn et al,[9] using a similar dose of naloxone, failed to precipitate angina in patients with silent ischemia during exercise testing. Furthermore, the investigators could not confirm that naloxone influenced the pain threshold in patients with reproducible effort-induced angina.

From these results, it is certainly possible that endorphins modify pain perception in patients with and without silent ischemia, and that other factors are responsible for the differences in pain sensitivity. Because the mechanism responsible for painless ischemia may be different in some patients than in others, conflicting results in studies evaluating the effects of naloxone may be due to patient selection. Also, the dose of naloxone used in these studies may not be adequate enough to block the relevant receptor sites.

In brief, there is good evidence to suggest that patients with painless myocardial ischemia have defective pain perception. In some cases, this defect is influenced by naloxone.

Beta-Endorphin Activity in Patients with Angina Versus Silent Ischemia: Study Design and Results

To test the hypothesis that endorphin secretion during exercise is related to the perception of chest pain in patients with coronary disease and angina, we measured plasma β-endorphin levels by radioimmunoassay before and after exercise in 25 patients with ischemia manifested by angina, a positive treadmill test result, and/or a positive result during exercise radionuclide study.

All patients rested at baseline for 1 to 2 hours. A supine radionuclide study was performed and blood obtained for β-endorphin analysis. Additional samples were obtained for endorphin analysis immediately after the patient performed a symptom-limited supine exercise test.

Overall results showed that the mean postexercise level of plasma β-endorphin—6.5 pmol/liter—was significantly higher than the baseline level of 4.92 pmol/liter. Fifteen patients had chest pain during exercise and 10 remained asymptomatic despite electrocardio-

TABLE II Correlation Between Plasma Endorphin Levels and Various Physiologic Parameters. Poststress Endorphin Levels Show a Positive Correlation with Time to Onset of Angina and a Negative Association with Occurrence and Duration of Angina

	Rest Endorphin	Poststress Endorphin	Difference
Angina	−0.24 (0.24)	−0.41* (0.04)	−0.24 (0.25)
Duration of angina	−0.35 (0.08)	−0.39* (0.05)	−0.15 (0.48)
Time to onset of angina	0.29 (0.16)	0.43* (0.03)	0.22 (0.28)
Maximal ST depression	−0.04 (0.86)	0.05 (0.81)	0.05 (0.81)
Time to ST depression (1 mm)	0.05 (0.81)	−0.08 (0.71)	−0.11 (0.62)
Rest ejection fraction (%)	0.29 (0.17)	0.48* (0.02)	0.28 (0.18)
Stress ejection fraction (%)	0.15 (0.48)	0.17 (0.42)	0.03 (0.88)
Peak work load (kpm/min)	−0.08 (0.69)	0.08 (0.71)	0.14 (0.50)

* $p \leq 0.05$.
Numbers in parentheses are p values.

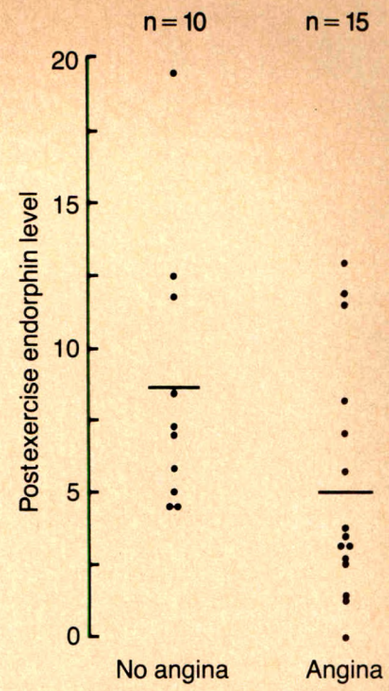

FIGURE 1. Postexercise plasma β-endorphin levels in patients who did not have angina vs those who did. The mean value in patients with angina is approximately 41% lower than it is in patients without angina despite considerable overlap.

TABLE III Summary of Studies Investigating the Plasma β-Endorphin Response in Patients with Myocardial Ischemia

	Glazier et al 1986[11]	Weidinger et al 1986[12]	Heller et al 1987[13]	Sheps et al 1987[10]
Subjects	6 asymptomatic 5 symptomatic	1 type I 4 type II 5 type III (2 post–MI) 6 normals	On exercise test: 10 anginal 12 angina-free (4 type I; 8 type II) 10 normals	25 anginal on exercise (22 in daily life; 16 post–MI)
Type test	Cold pressor Electric skin stimulation Ischemic forearm tourniquet test	2 symptom-limited upright bicycle tests, the 2nd after naxolone	Treadmill after 1 hour relaxation	Supine bicycle exercise
Blood	Baseline & at tolerance time for forearm ischemic pain	Rest, peak exercise, & 5 mins after recovery	Before, every 3 min during, & 10, 20 & 30 min after exercise	Immediately before & after exercise
Radioimmunoassay	Per Clement Jones et al and Jeffcoate et al*	New England Nuclear Kit	Immuno-nuclear Corp.	Immuno-nuclear Corp.
Results	β-endorphin levels similar during basal state & induction of forearm pain in both groups	Slight but no significant increase in β-endorphin levels postexercise in CAD pts and controls; no angina	β-endorphin levels elevated postexercise in all groups	Poststress β-endorphin levels significantly lower in anginal pts than in asymptomatic pts; positive correlation w/time to onset

CAD = coronary artery disease; MI = myocardial infarction; w/ = with.

* Clement-Jones V, Lowry PJ, Rees LH, Besser GM. Metenkephalin circulates in human plasma. Nature 1980; 283:295–297. Jeffcoate WJ, Rees LH, Lowry PH, Hope J, Besser GM. β-lipotrophin in human plasma and cerebrospinal fluid: radioimmunoassay evidence for γ-lipotrophin and β-endorphin. J Endocrinol 1978; 77:27P–28P.

graphic evidence of ischemia lasting an average of 3 minutes. A comparison of β-endorphin levels in those who had angina vs those who did not showed that β-endorphin levels were 41% lower in the angina group (Fig. 1). Postexercise β-endorphin levels were negatively correlated with occurrence and duration of angina and positively associated with time to onset of angina. No relation was found between endorphin levels and maximal heart rate × blood pressure product, work load, total work performed or ST-segment depression (Table II).[10]

Results of Other Investigations

Several other studies have measured plasma β-endorphin levels as a means of examining pain mechanisms in patients with coronary disease (Table III). Glazier et al[11] compared pain perception in patients with silent myocardial ischemia and chronic stable angina. Patients were divided into 2 groups, according to whether painless (group A) or painful ischemia (group B) was predominant. Patients in group A had episodes of ST-segment depression that were greater than 2 mm, occurring during 2 or more exercise tests; over 90% of episodes during repeat Holter monitoring were painless. Those in group B had more than 50% of episodes of ST depression occurring with pain during repeat Holter. Study participants were subjected to such stressors as cold pressor tests, ischemic forearm tourniquet tests and electrical stimulation.

Group A had a significantly higher threshold and tolerance for all stressors. The investigators compared β-endorphin, met-enkephalin, noradrenalin and adrenalin levels at basal state and during pain tolerance between both groups. There were no significant differences, and no correlation was obtained between these levels and pain characteristics. However, the investigators did not measure endorphin levels or any other hormones during spontaneous or exercise-induced ischemia.[11]

Weidinger et al[12] studied endorphin levels in 10 patients, 5 of whom were asymptomatic and 5 of whom had a mixed classification of type III chest pain. Patients performed 2 symptom-limited, submaximal bicycle exercise tests. Blood samples were obtained at rest, peak exercise and 5 minutes after recovery. Five minutes before the second test 1.2 mg of naloxone was injected. None of the study participants had angina, with or without naloxone, and patients in both groups had slightly higher β-endorphin levels during exercise.[12].

Heller et al[13] evaluated 3 groups of patients: normal control subjects, those with coronary disease and no history of angina, and those with coronary disease and exercise-induced angina. Patients exercised submaximally to the onset of angina. Blood samples were obtained immediately before exercise, every 3 minutes during exercise, and 10, 20 and 30 minutes after exercise. The groups demonstrated no differences in their β-endorphin response to exercise, all having a significant increase within 10 minutes after exercising.[13]

Conclusions

Differences in these study results could be due, in part, to discrepant or insensitive radioimmunoassay techniques, since some assays exhibit significant cross-reactivity to nonopioid peptides. Variation in patient populations—particularly in psychological profile, amount of baseline ischemia or degree of physical conditioning—is another possible source for inconsistency. The time of day that studies were performed and blood samples were obtained is also important, because β-endorphin levels are known to peak during morning hours[14]—the same time when ischemic activity is highest.[15]

It is hoped that further investigation will produce more consistent results and will clarify the role of endorphins in silent ischemia. Additional knowledge about defective pain perception in patients with asymptomatic coronary disease may hold the key to early and more effective diagnosis.

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Discussion I

Dr. Cohn (*Stony Brook, New York*): That was an excellent overview, Dr. Sheps. The most striking observation is the degree of overlap in endorphin values in the various studies, and I wonder if we really are ever going to find a sharp differentiation.

Dr. Friesinger (*Nashville, Tennessee*): Dr. Sheps, can you comment further on endorphins and their measurement? Considering the large number of endorphins, in addition to their short half-life and extensive cross-reactivity, it certainly appears that evaluation could be a big problem.

Dr. Sheps (*Chapel Hill, North Carolina*): I agree. Three basic classes of endorphin peptides have been identified: β-endorphins, which are the most potent endogenous opioid peptides known; met-enkephalins; and the dynorphins. All 3 of these compounds are secreted in response to stress, both centrally and peripherally. We also know that there is a general relationship between analgesia and elevation in peripheral and central nervous system levels of β-endorphins and met-enkephalins. The role of dynorphins—including their analgesic potential—has not yet been defined. Obviously, the differences in radioimmunoassay techniques are important. The recent realization of the potential for cross-reactivity with nonopioid compounds has led to the development of assay techniques that are specific for β-endorphins and met-enkephalins. As you mentioned, half-life contributes to variable study results. The half-life of β-endorphin in the plasma is approximately 20 minutes. Improper timing of blood samples could result in erroneous measurement. One final point about endorphin studies is, very simply, are the correct substances being measured? Very few—in fact, none—of the studies have measured met-enkephalin levels during exercise or spontaneous ischemia. It may be that met-enkephalin, which is secreted by the central nervous system and the adrenal gland, is very important to pain perception. So, obviously, more work needs to be done if we are going to find an answer to these questions.

Dr. Krucoff (*Washington, D.C.*): Some of the information Dr. Sheps discussed may account for the phenomenon of walk-through and run-through angina that we are currently seeing in our health- and fitness-conscious society. Clearly, β-endorphin levels can be elevated with chronic conditioning. This may account for the ability of the marathon runner to push himself to the point of sudden death, without any ancillary warning signs or signals to slow down. The technical aspects of measuring these substances have given us conflicting information, but I think this area is an interesting and important one to pursue.

Dr. Pepine (*Gainesville, Florida*): One of the most significant correlations of Dr. Shep's study was between endorphin levels and duration of exercise to onset of angina. A key question appears to be, "What is the relationship between the onset of ischemia and the onset of anginal pain?" Are there any data examining the association between onset of ST depression and onset of angina in these individuals? In other words, do people who have ischemia marked by ST-segment shift, with a very short interval between ST-segment shift and perception of pain, have low endorphin levels compared with those who can exercise for several minutes after the onset of significant ST-segment depression before they have pain?

Dr. Sheps: That is a very good question . . . one that I have no data on. The correlations that we made with ST-segment depression were really examining time to 1 mm of ST-segment depression. In both patients with painful and painless ischemia, we found no relationship. All of our patients did have ST-segment depression for at least 2 minutes, whether or not they experienced angina. But we did not really look at endorphin levels and onset of angina—and that is obviously worthwhile doing.

Dr. Silber (*Birmingham, Alabama*): That's always a question I've had. One of the differences between the United States and Europe is that European anti-ischemic interventions are aimed at ST depression as an endpoint, whereas in the United States, therapeutic efficacy is determined by the onset of angina only. Since these endorphin studies have shown that angina is so subjective—unlike ST-segment depression—wouldn't you say that angina is a less reliable parameter for estimating anti-ischemic efficacy?

Dr. Sheps: Yes, certainly. But angina is still the only approved indication for treatment. Hopefully, that will change in the near future.

Dr. Kontos (*Richmond, Virginia*): Dr. Sheps, it seems to me that results of endorphin assay would vary according to the site involved. Isn't it possible that the really important concentration of endorphins is in the brain, and that if cerebrospinal fluid were measured, there might be a better correlation of results?

Dr. Sheps: That's obviously a good point. I would like to know what the endorphin and enkephalin levels are in the cerebrospinal fluid and also in the brain tissue itself, because even spinal fluid may not reflect what's occurring in the brain or dorsal horn of the spinal cord, where endorphin modulation appears to be centralized. Obviously, it is not practical to do this. There is a general relationship between plasma and brain levels of endorphins—at least in animals. These associations haven't been examined in man. But it certainly is possible that we are not measuring endorphin levels in the best location.

Dr. Kupersmith (*Louisville, Kentucky*): Do any of the antianginal agents we prescribe have an effect on endorphin levels?

Dr. Sheps: To my knowledge, no one has really examined that. Investigators who have studied patients on stable doses of medications have not found any correlations or differences among patient groups, according to levels of different drugs. I am not aware of any specific effect of medication on these parameters, other than nonpharmacologic agents such as caffeine, which can affect endorphin levels.

Six-Year Survival of Patients With and Without Painless Myocardial Ischemia and Out-of-Hospital Ventricular Fibrillation

BIMLENDRA SHARMA, MD, and RICHARD P. WYETH, MA

Out-of-hospital ventricular fibrillation (OHVF) is the most common cause of sudden cardiac death. Of 1,070 patients with OHVF who entered this study, 150 were discharged alive. Of this group, 120 were free of anoxic brain damage. Of these survivors, 67 (57%) had no previously demonstrated anginal symptoms. Treadmill stress testing revealed painless ST depression in 76% of these neurologically intact patients. Exercise ventriculography in a subset of 9 patients without angina before OHVF and in 6 patients with typical anginal symptoms revealed marked left ventricular dysfunction with ST depression in the absence of chest pain in all 15 patients. Sublingual nitroglycerin reversed this evidence of ischemia in the asymptomatic patients. Patients were followed for 6 years after discharge. No statistical difference in mortality could be demonstrated for patients who had previous anginal symptoms vs those who did not, nor was age a predictor of mortality. Women had the same risk of death as men at 2 years after OHVF, but a significantly higher risk by year 6. Myocardial infarction associated with OHVF did not predict lower mortality throughout the study. **(Am J Cardiol 1988;61:9F–12F)**

Sudden death, described over 2,000 years ago by Hippocrates, continues to be a major problem associated with heart disease. Out-of-hospital ventricular fibrillation (OHVF) is the most frequent cause of sudden cardiac death.[1] Whereas there is considerable controversy over the exact pathophysiologic mechanisms, myocardial ischemia appears to play a pivotal role in precipitating most episodes of OHVF.[2] Recent evidence suggests that myocardial ischemia in survivors of OHVF may be painless, whether or not these patients have preliminary angina pectoris.[3] This current study reports on survival of 1,070 patients who experienced OHVF, and compares the hemodynamics of a subset of survivors with and without previously diagnosed symptoms of coronary artery disease.

Methods

Study participants consisted of 1,070 patients who experienced out-of-hospital sudden cardiac death due to ventricular fibrillation, demonstrated on monitor strips obtained by emergency medical technicians. Concomitant occurrence of myocardial infarction (MI) with OHVF was determined independently by 3 cardiologists on the basis of creatine kinase-MB enzyme levels and serial 12-lead electrocardiographic data; in questionable cases, a technetium-99m pyrophosphate scan was also done. Patients were then classified as having definite MI, no MI, or uncertain MI associated with the admission episode of OHVF. Study participants were also grouped according to whether angina pectoris was present (symptomatic) or absent (asymptomatic) before the admission episode of OHVF.

A total of 150 patients survived hospitalization, 120 (11%) of whom avoided hypoxic brain damage (Table I). Before discharge, 108 of the 120 neurologically intact survivors underwent treadmill stress testing using standard Bruce protocol (stress testing was contraindicated in 12). A small subset of this group also underwent exercise ventriculography as an essential part of diagnosis 2 to 4 weeks after ventricular fibrillation.[3,4]

All patients were discharged on standard antiarrhythmic drug therapy. Of the 120 neurologically intact survivors, 3 were lost to follow-up. The remaining 117 were followed biannually for 6 years through personal interview or telephone inquiry to either the patient or the patient's physician, or both. Survival curve analy-

From the Cardiology Care Clinic for St. Joseph's Hospital and National Park Medical Center, Hot Springs, Arkansas, and Division of Cardiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas.

Address for reprints: Richard P. Wyeth, MA, University of Arkansas for Medical Sciences, Division of Cardiology, 4301 West Markham, Slot 532, Little Rock, Arkansas 72205.

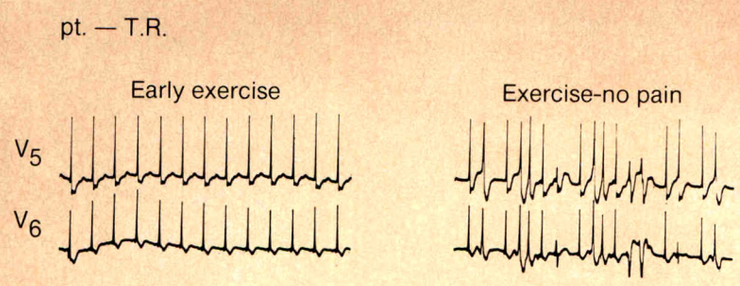

FIGURE 1. Electrocardiogram (leads V_5–V_6) from a survivor of out-of-hospital ventricular fibrillation during a treadmill stress test using the Bruce protocol. Early exercise (stage I) showed normal sinus rhythm with ST depression. At stage II (exercise, no pain), ST depression increased and ventricular ectopy developed in the patient.

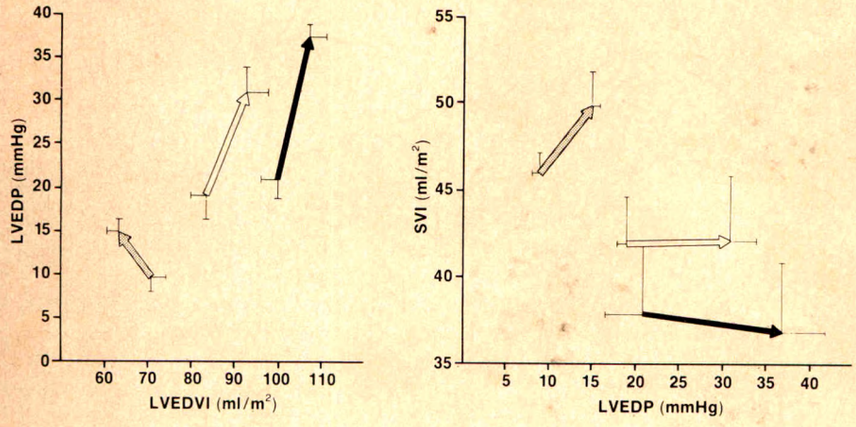

FIGURE 2. Changes in left ventricular end-diastolic pressure (LVEDP)-volume relation from rest to exercise (*left*), and changes in a modified Frank-Starling function curve (*right*). *Open arrows* show the direction of change seen with exercise in asymptomatic patients, symptomatic patients (*closed arrows*) and normal subjects (*stippled arrows*). The direction of change for both asymptomatic and symptomatic patients is markedly different from normal subjects and indicates severe diastolic and systolic dysfunction with exercise in survivors of out-of-hospital ventricular fibrillation. LVEDVI = left ventricular end-diastolic volume index; SVI = stroke volume index.

TABLE I Hospital Course of Patients with Out-of-Hospital Ventricular Fibrillation

Patient Status	Number	%
Brought to ER	1,070	100
Declared dead in ER	745	70
Transferred to CCU	325	30
Discharged alive	150	14
Neurologically intact	120	11
Anoxic brain damage	30	3

CCU = cardiac care unit; ER = emergency room.

sis used the method of Cutler and Ederer.[5] Chi-square analysis and Student *t* test were used as appropriate.

Results

Results of predischarge treadmill stress testing showed ST-segment depression without angina in 91 patients (76%); in 10% of patients, angina accompanied ST-segment depression. In 17 patients (14%) there was no ST depression. Of these 91 patients, 36 (40%) had, with further exercise, evidence of ventricular ectopy associated with painless myocardial ischemia. No patient had dysrhythmia without evidence of myocardial ischemia (Fig. 1).

In 15 of the neurologically intact survivors (9 asymptomatic, 6 symptomatic), exercise ventriculography was performed. A decrease in both diastolic and systolic left ventricular function was observed during submaximal exercise in both groups (Fig. 2). This exercise was painless in all 15 patients, despite a significant increase in ST depression in asymptomatic patients. When sublingual nitroglycerin was given to 6 of these asymptomatic patients and a second but identical exercise test completed, there was a reduction in left ventricular end-diastolic volume, from 102 ± 24 ml/m^2 to 81 ± 19 ml/m^2 (difference not significant). End-systolic volume also decreased, from 57 ± 15 ml/m^2 to 36 ± 16 ml/m^2 ($p < 0.008$). This improvement in left ventricular function was accompanied by a significant reduction in ST depression, from 0.24 ± 0.16 mV to 0.07 ± 0.14 mV ($p < 0.01$) and was reflected in the improvement of stroke volume, from 43 ± 9 ml/m^2 to 50 ± 7 ml/m^2 ($p < 0.01$). Thus, these asymptomatic patients showed hemodynamic and electrocardiographic improvement with nitroglycerin, despite the lack of typical angina pectoris (Fig. 3).

Two years after discharge, 85 of the 117 patients (73%) were alive. Of the 32 patients who died, 26 (81%) subsequently succumbed to sudden cardiac death, 4 had congestive heart failure and 2 died from noncardiac causes (Fig. 4). By year 6, an additional 34 survivors of OHVF had died. Of these 34 deaths, 8 (24%) were sudden cardiac death. Thus, overall survival for these patients was 44% at 6 years. Of the 56% mortality rate observed at 6 years, 30% of all deaths could be attributed to another episode of OHVF. MI associated with the admission episode of OHVF did not influence long-term survival and was not protective (Fig. 5).

Survival for symptomatic and asymptomatic patients at 2 and 6 years was similar. There was no difference in the percentage of female vs male survivors at 2

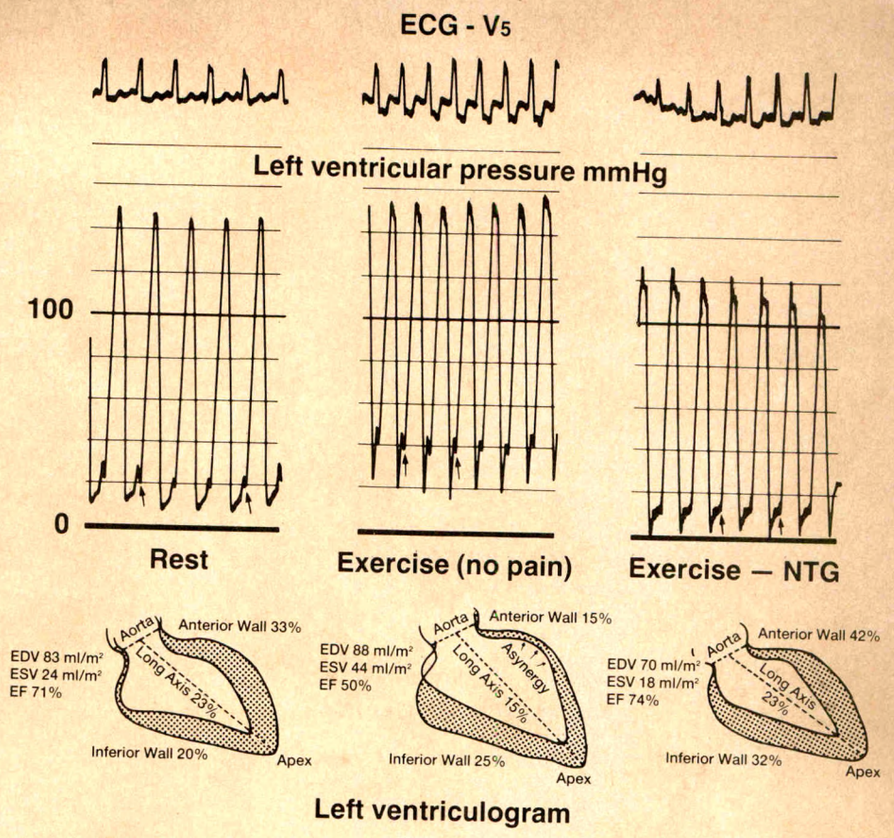

FIGURE 3. Simultaneous recording of chest lead V_5, left ventricular pressure, and ventriculogram from an asymptomatic patient during supine bicycle exercise indicating electrocardiographic, hemodynamic and left ventriculographic evidence of painless myocardial ischemia. Note the development of ST depression, increased end-diastolic pressure (*arrows*), decreased ejection fraction, and development of anterolateral asynergy with exercise. A reversal of this global and regional left ventricular dysfunction was seen at exercise after 150 μg of sublingual nitroglycerin (NTG). ECG = electrocardiogram; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume.

years, but by year 6, there was a marked increase in deaths among women. Age was nondiscriminatory at both 2 and 6 years (Table II).

Discussion

This study shows that sudden cardiac death associated with OHVF is profoundly morbid, with only 30% of patients surviving the initial event. About half of those who initially survived OHVF in our study died in the hospital. This is similar to earlier reports.[6]

The current results indicate that MI occurs in at least half of the patients who survive OHVF. Data from studies done in survivors may be more reliable than than those obtained by trying to determine the occurrence of myocardial ischemia in those who die from OHVF.[2] Our findings further suggest that the concomitant occurrence of MI with an episode of OHVF does not alter the prognosis for 6-year survival. This differs from the classic works of Baum et al[7] and Schaffer and Cobb.[8] This contrast may be due to the difference in enzymatic criteria for MI, which, in 1974, used lactate dehydrogenase and serum glutamate-oxaloacetate transaminase instead of the more definitive creatine kinase-MB currently used.

Our results from survivors of sudden death suggest that while women who experience OHVF are at the same risk for cardiac death 2 years after the event, they are at significantly higher risk than their male counterparts by the sixth year. It is well documented that men are at a much higher (approximately 4-fold) risk for sudden death than women.[9] The women in our study

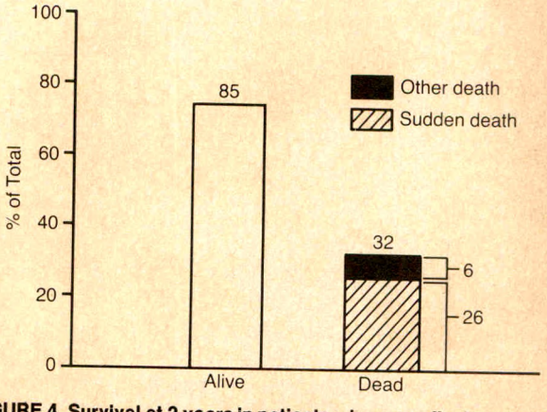

FIGURE 4. Survival at 2 years in patients who were discharged after an episode of sudden cardiac death associated with out-of-hospital ventricular fibrillation. The numbers *above* and to the *right* of the bar graphs are numeric totals.

may also represent an atypical cohort by virtue of their entry into the study. It is also possible that the small number of women in this study has produced a statistical artifact due to small sample size. The results of the current study do indicate that once an episode of OHVF has occurred, there is no statistical difference in survival, from the time of hospital discharge to the sixth year, in patients with either typical symptoms of angina or painless myocardial ischemia.

The induction of dysrhythmia with treadmill exercise as seen in this study was invariably associated

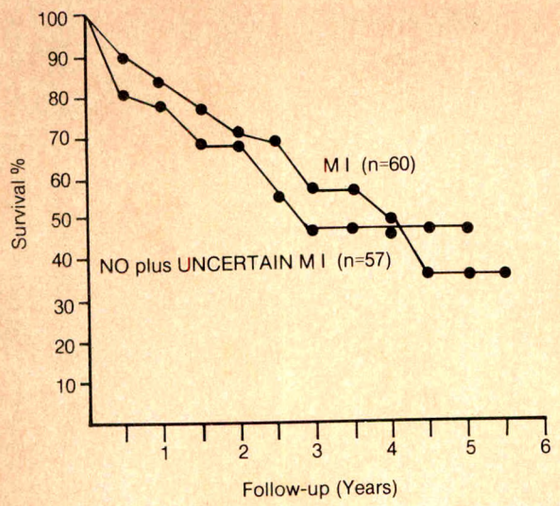

FIGURE 5. Long-term survival curve of patients with concurrent myocardial infarction (MI) and out-of-hospital ventricular fibrillation. Regardless of status, there was no statistical difference in survival throughout the follow-up period.

TABLE II Six-Year Prognosis by Group in Survivors of Out-of-Hospital Ventricular Fibrillation

Group	Number (% of Total Survivors at Discharge)	Number (% Survival of Group)	
		Year 2	Year 6
Total	117 (100)	73 (85)	44 (51)
Men	102 (87)	73 (74)	48 (49)
Women	15 (13)	11 (73)	2 (13)*
Asymptomatic	67 (57)	67 (45)	39 (26)
Symptomatic	50 (43)	80 (40)	50 (25)
<49 years	11 (9)	11 (100)	9 (82)
≥49 years	106 (91)	70 (74)	40 (42)

* $p < 0.01$.

with electrocardiographic evidence of painless myocardial ischemia. Experimental evidence has demonstrated that acute ischemia and submaximal exercise may induce ventricular fibrillation.[10] There is also recent clinical demonstration of ventricular fibrillation induced by painless myocardial ischemia during exercise testing.[11] Evidence shows that myocardial ischemia may be painless, yet produce marked left ventricular dysfunction in patients with and without documented coronary artery disease.[3]

Severe coronary artery disease is found in most patients after OHVF, both in those who survive and those who do not.[2,12] Sudden cardiac death may result from coronary artery disease that induces platelet aggregation, which in turn causes vasospasm and thrombus formation.[13–15] In fact, it has been possible to prevent ventricular fibrillation in a canine model of sudden cardiac death by preventing coronary thrombosis with prostacyclin.[16] The duration of such vasospasm or thrombic coronary occlusion, or both, may thus determine if MI is associated with sudden cardiac death.

From their survey of trials on the use of platelet-suppressive drugs after MI, Gelman and Mehta[14] suggest that the use of antiplatelet therapy in post-MI patients at high risk for sudden death may be beneficial. Based on current data, it may be advantageous to offer all survivors of OHVF a therapeutic regimen that includes antiplatelet agents and vasodilators.

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Discussion II

Dr. Kennedy (*St. Louis, Missouri*): Dr. Sharma, I was looking at the defibrillation data. One of the things that immediately comes to mind is the Medic I study in Seattle.[1] Schaffer and Cobb reported a mortality of 25% to 35% in the first year for patients with primary ventricular fibrillation—not associated with myocardial (MI) or secondary ventricular fibrillation—who had no associated infarction. The group that sustained necrotic damage had a much lower mortality. Did you have a reason why?

Dr. Sharma (*Little Rock, Arkansas*): Schaffer and Cobb, as well as Baum, collected their data in 1974.[1,2] At that time, the diagnosis of MI was not as accurate as it is currently. The data I presented specifically addressed the lack of difference in mortality rates between patients with and without MI. Our diagnosis of MI was based on the independent observations of 3 cardiologists, unaware of the others' interpretations. Serial electrocardiogram (ECG) and creatinine kinase MB (CK-MB) enzyme determinations were analyzed. If the diagnosis was not unanimous, technetium-99 pyrophosphate scintigraphy was done. Even then, we were not able to determine if MI had occurred in 14 of the 117 patients we followed. That is, in 12% of our patients, we could not be certain if enzyme increases were due to resuscitation, with minimal or no ECG changes.[3] Our data seem to indicate that MI affords no protection. The incidence of sudden death through the sixth year of this study was no different for patients who had concomitant MI vs those who did not.

Dr. Kennedy: So your findings are consistent when you divide the 2 subpopulations?

Dr. Sharma: Yes, I am not sure that the 1974 diagnosis of certain infarction or no infarction, based on serum glutamic-oxaloacetate transaminase/lactate dehydrogenase, was as reliable as it is currently, using CK-MB. This may account for the difference in mortality in our vs Schaffer and Cobb's data.

Dr. Kennedy: During exercise, did the presence or absence of ST-segment changes in any subpopulation influence outcome?

Dr. Sharma: We had ST-segment changes in 76% of patients during submaximal exercise.[3] Had we exercised patients maximally—which we didn't do because we wanted to approximate a real-life situation—we might have seen more ST-segment changes.

Dr. Sheps (*Chapel Hill, North Carolina*): How do you relate finding evidence of silent ischemia in the majority of the survivors of sudden death to the relatively rare occurrence of serious arrhythmia in patients with a lot of silent ischemia before sudden death? If frequent episodes of silent ischemia are a risk factor for arrhythmic sudden death, why aren't we seeing more arrhythmias in patients with a lot of silent ischemia?

Dr. Sharma: I don't have an answer to that. But over 6 years of follow-up, we have seen cardiac arrest recur in many of these patients (27%). There is a matter of timing—ischemia during exercise and arrhythmia have to be timed in a certain manner for sudden death to occur.

Dr. Cohn (*Stony Brook, New York*): I would also like to answer that question, because it comes up repeatedly. In other words, if silent ischemia is so bad, why don't we see more ventricular tachycardia with it? We have to look at the other side of the coin. How often does ventricular tachycardia occur with angina? Not often, yet it is the patient with angina and coronary atherosclerosis who is going to develop ventricular fibrillation or some other manifestation of electric instability. To find a link in a given situation is unusual, however. Dr. Sharma obviously was looking from the retrospective side—his patients had "died." How to recognize which patients are going to progress to sudden death is, of course, the $64,000 question. Dr. Sharma was able to show a sudden death population that had no history of heart disease, but definitely had silent ischemia. We don't know whether his patients had silent ischemia before sudden death, but autopsy data in other studies have shown not only extensive atherosclerosis, but also scars of small infarctions that went unrecognized. We need a combination of prospective and retrospective data to make the case as convincing as possible. I should add, too, that other investigators have data similar to yours, Dr. Sharma, but they have not yet reported them.

Dr. Beller (*Charlottesville, Virginia*): In a study undertaken at the University of Virginia, we looked at a group of 38 patients with recurrent sustained ventricular tachycardia. Symptom-limited stress thallium-201 testing confirmed that very few had exercise ischemia. Also, in this study, there was no difference in the prevalence of thallium-201 redistribution in those who did or did not have exercise-induced ventricular tachycardia.[4] In contrast, patients who had out-of-hospital cardiac arrest or who developed exercise-induced ventricular fibrillation on treadmill testing had a higher prevalence of ischemia compared with those with inducible sustained ventricular tachycardia. Patients with sustained ventricular tachycardia who are inducible during exercise testing usually have marked myocardial damage, characterized by a significantly decreased ejection fraction, multiple persistent thallium-201 defects consistent with myocardial scar, and very little thallium-201 redistribution.

Dr. Stern (*Jerusalem, Israel*): It is very important that the possible association between ischemia and arrhythmia came

up during this meeting. For the past 15 years I have been searching for such a link, to no avail. In this audience, we have personal experience of tens of thousands of ischemic episodes, and anyone who has seen an ischemic episode that continues with arrhythmia should raise his hand. I can't raise mine. This relationship between arrhythmias and ischemia came up recently during a Holter monitoring workshop at an internationally attended arrhythmia meeting. Those present also confirmed that they rarely, if ever, see an association between ischemia and arrhythmia. So I think that we have to relinquish the concept that arrhythmia induces ischemia or vice versa.

Dr. Deanfield (*London, England*): I would agree with Dr. Stern that the association between transient ST-segment depression and malignant ventricular arrhythmias—if present at all—is very loose and not strongly related to the cause of death in these patients. We have to try to differentiate between a frequent phenomenon in patients with coronary artery disease and the end-stage event, which can only happen once. There is a very poor association between transient ST-segment depression and the end event. That doesn't tell us that the final event in these patients is not associated with a very severe ischemic insult, and long-term follow-up sometimes reveals evidence of transmural myocardial ischemia and ST-segment elevation. Those patients have a very poor prognosis; in their situation, the association between ST elevation and ventricular tachycardia is much tighter than it is with frequent episodes of transient ST-segment depression. So the lack of good correlation between ST depression and malignant ventricular arrhythmias doesn't say anything about what is happening as the terminal event in those patients. It may still be related to severe transmural myocardial ischemia as an end event.

Dr. Cohn: The problem of sudden death in the general population is a real one. We've estimated in this country, for example, that at least 50,000 people a year die suddenly who have no previous history of cardiac disease, and yet at autopsy have extensive disease. There's a distinct population at risk, and even though there are technological, ethical and practical problems about identifying these patients before they present with infarction or death, it is not acceptable for us to simply to throw up our hands and say, "Well, the problems are insurmountable, so let's look at something else."

Dr. Sharma: The same thing has bothered me for a long time. During angioplasty, we find that while the chest ECG may not show evidence of ischemia, other epicardial leads show tremendous ST elevation/ST depression.[5,6] It is possible that surface ECGs do not always show evidence of myocardial ischemia.

Dr. Deanfield: That isn't actually the issue here, because you are detecting it, but are failing to show an association. All I'm saying is that the lack of close relationship between transient ST-segment depression and ventricular arrhythmias during everyday activities should not detract us from the concept that the terminal event may be related to transient ischemia. Those are not mutually exclusive observations.

Dr. Silber (*Birmingham, Alabama*): Yes, but whether the terminal event might still be related to ischemia is hypothetical. I agree with Dr. Stern's belief that ischemia is not related to arrhythmias. The same is true of exercise-induced ischemia. My colleagues and I have studied over 300 patients with proven coronary artery disease and significant ST-segment depression during exercise after withdrawal of all anti-ischemic medication, and only 1 of these had ventricular fibrillation during exercise testing.

Dr. Krucoff (*Washington, D.C.*): I think we have to consider 2 other terms: the very significant majority vs a potentially significant minority. I agree with Dr. Stern that no one would claim to have frequently seen an association between ST changes and arrhythmias. On the other hand, we certainly see plenty of association between reperfusion phenomena and arrhythmias. This is closer to what Dr. Deanfield was mentioning, namely, that transient, very severe, transmural myocardial ischemia, when suddenly relieved (which clearly happens endogenously through spasm or platelet-mediated thrombosis and sudden reperfusion), can result in very profound primary ventricular fibrillation and other arrhythmias. That's clearly not the majority of people in whom we document ischemic episodes, but it is at least a significant minority of persons in whom some sort of intervention is very important.

Dr. Friesinger (*Nashville, Tennessee*): The exercise test is, by any criteria, a relatively poor diagnostic test for ischemia. However, at least in stable subsets, it's a relatively powerful prognostic tool, in terms of what we can learn from the exercise load and duration.

Dr. Cohn: There is a definite incidence of coronary disease and fatal events in people who have negative exercise tests. The risk ratio is obviously much higher in those with the positive test, but those with negative tests also are having events, and they outnumber the positive responders in sheer volume. The question is whether the exercise test is missing the diagnosis, which is certainly possible. My point is that, if we recommend cardiac catheterization for asymptomatic patients, we should have very strong noninvasive evidence of disease before subjecting people to the risks of the procedure. I don't have any answer yet on how to approach the patient we suspect of being at risk but who has negative, noninvasive indices. Yes, some of those people will go on to disease, but I'm much more concerned with the patient who has a positive noninvasive test. Someone once said to me, "Well, sudden death is fine. I mean, it's a quick, painless end, so therefore we shouldn't be that concerned with it." And it's true that it's not a bad way to die when you are 75 or 80, but not when you're 40 or 45. That's why I feel we're obligated to continue to investigate, even though it's fraught with problems. Dr. Becker, did you have any comments?

Dr. Becker (*Baltimore, Maryland*): I would agree with that idea. The more we know, the easier it will be to finally make these decisions. In terms of the clinical care of a patient, I agree that it would not be desirable to catheterize everybody who, by virtue of age or risk factors, is in a high-risk group. We'd like noninvasive tests to specifically indicate that the patient has an increased likelihood of having cardiac disease. We obviously need to continue our efforts at technological improvements to facilitate detection. Hopefully, tomographic thallium is one approach to this problem, but it has problems as well.

Dr. Pepine (*Gainesville, Florida*): One of the topics that's come up repeatedly, relative to both silent and painful ische-

mia, is what the signal is for pain, and whether or not the heart is sending out a signal. My understanding of nociceptive receptors is that they respond to either metabolic stimuli or changes in mechanics. Long ago, metabolic stimuli for pain perception were ruled out, relative to the heart, leaving the possibility of a mechanical stimulus. Could a change in left-ventricular diastolic properties, reflected in end-diastolic pressure or left atrial pressure, be the mechanical stimulus for pain perception? Your data show very clearly that these people have a tremendous rise in left-ventricular end-diastolic pressure during exercise without reporting pain, so it's probably not the absolute pressure, but could some characteristic of the pressure change or the end-diastolic volume change account for pain perception?

Dr. Sharma: I don't have these data, but I do have a group of patients who were first exercised submaximally with no ischemia, and showed a rise in left-ventricular diastolic pressure that was almost abnormal. They continued to exercise, had another left ventriculogram run, and had angina. But, the hemodynamics, volumes, and pressures were higher in that group. The same asymptomatic submaximal exercise test in coronary artery disease can become symptomatic during continued exercise.

Dr. Amsterdam (*Davis, California*): I would like to refer back to the ischemia-arrhythmia issue. The relative lack of ventricular ectopic activity with exercise-induced ischemia doesn't eliminate ischemia, *per se*, as a cause of arrhythmias. Exercise is a complex function with inhibitory (ie, tachycardia) and provocative (ie, ischemia, sympathetic activation) effects on ventricular ectopic activity, and the occurrence of arrhythmias is a function of the interplay between these factors. There are examples in the literature of the association between ischemia and lethal arrhythmias during ambulatory ECG monitoring.[7] The relationship is unclear, but appears to be definite in some instances. Also, as Dr. Cohn says, absence of arrhythmias during ST-segment alteration on ambulatory ECG does not preclude an association between these factors in the final clinical event. It may depend on the presence of the proper constellation of factors at a given time. Dr. Sharma's data relate to this issue. It is not surprising that patients with coronary artery disease who have survived cardiac arrest have silent ischemia. The latter is prevalent in a majority of the coronary population as a whole, and therefore, in itself, does not identify risk of sudden death. So, as has already been stated here, we are currently unable to identify the patient with silent myocardial ischemia who is at increased risk for sudden death.

Dr. Sharma: I agree. What I have shown today is the association of ischemia in patients with sudden death from ventricular fibrillation. But, during our treadmill testing, I also showed that stage I patients have ischemia, and stage II have multiple bizarre arrhythmias, but it doesn't happen in every patient we exercise. As you said, timing and situation have to be there, and the considerations are multifactorial.

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Clinical Outcome of Silent Myocardial Ischemia

SHLOMO STERN, MD, ALEX GAVISH, MD, DAN ZIN, MD, and DAN TZIVONI, MD

Asymptomatic coronary artery disease can be detected by an abnormal electrocardiogram at rest, by a positive exercise test result unaccompanied by pain, or by the demonstration of silent ischemic episodes during daily activities. However, the clinical outcome of patients with silent myocardial ischemia has not yet been clearly defined. In a study of 356 patients with documented coronary disease—211 of whom had previous myocardial infarction—the prognostic information of spontaneous ST-segment depression was found to be independent of that associated with a positive exercise test result, ejection fraction, and extent of arteriographically documented coronary artery disease. Patients with asymptomatic ischemia had a higher coronary event rate than those without ischemia. Cardiac event rates followed a similar pattern for patients with silent, symptomatic and mixed ischemia—whether or not there was previous myocardial infarction.

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Asymptomatic coronary artery disease can be detected by an abnormal resting electrocardiogram (ECG), by a positive exercise test result unaccompanied by pain, or by the demonstration of silent ischemic episodes during daily activities. However, the clinical outcome of patients with silent myocardial ischemia has not yet been clearly defined. The ECG at rest enabled Froelicher et al[1] to diagnose silent ischemic heart disease in asymptomatic airmen. Subsequent study showed that many of these 78 airmen had significant occlusions in their coronary arteries, and that during an average follow-up period of 17 months, 22 had overt signs of ischemic heart disease, 4 had myocardial infarction (MI) and 2 died suddenly.[2]

Silent myocardial ischemia is frequently observed during exercise testing. ST depression, without accompanying pain, was detected in 50% of 540 patients who had a positive result during the Bruce protocol treadmill test.[3] In most of the patients who had chest pain ischemia preceded the pain. Weiner et al[4] analyzed the data of 2,982 patients from the Coronary Artery Surgical Study. They demonstrated that in patients with silent myocardial ischemia during exercise testing, the extent of coronary artery disease and the 7-year survival rate were similar to that of patients with symptomatic ischemia during exercise testing. The prognosis was determined primarily by the extent of coronary disease, and not by the presence or absence of pain during a positive treadmill test.

In a study from the National Institutes of Health involving 147 asymptomatic or mildly symptomatic patients, Kent et al[5] found a relatively low (3%) annual mortality rate. However, among asymptomatic patients with 3-vessel disease and poor exercise capacity, 20% died and another 20% had symptoms requiring coronary surgery during a mean follow-up period of 25 months. The investigators recommended that such patients undergo early coronary bypass surgery, even though they lacked symptoms. An updated follow-up study in this group showed that the prognosis of patients with silent or symptomatic ischemia during exercise testing was similar.[6]

Thallium-201 imaging was combined with treadmill testing by Walters et al.[7] Twenty-eight of their patients had silent ischemia and had the same hypoperfusion during stress as the 27 patients who had symptomatic ischemia. The silent group had an even higher incidence of MI and death than the symptomatic patients during 1-year follow-up. In 241 postinfarction patients, Gibson et al[8] studied the prevalence and prognostic significance of silent ischemia by thallium-201 exercise testing. The prevalence of silent myocardial ischemia in this study was 41% at 2 weeks after an uncomplicated infarction. Contrary to the results of other workers, these investigators found that asymptomatic ischemia correlated with smaller ischemic territories and less extensive coronary artery disease. During a follow-up period of 27 months, the frequency of cardiac events was lower in patients with silent

From The Heiden Department of Cardiology, Bikur Cholim Hospital, Jerusalem, Israel.

Address for reprints: Shlomo Stern, MD, The Heiden Department of Cardiology, Bikur Cholim Hospital, P.O. Box 492, Jerusalem 9100, Israel.

ischemia than in symptomatic patients. Kouz et al[9] found that silent ST depression during treadmill testing in 103 postinfarction patients was associated with the same extent of coronary disease, the same left ventricular function, and the same exercise duration as in 97 other patients with painful ST depression. These findings may provide the explanation for the similar prognosis of patients with and without pain.

An association between exercise-induced painless myocardial ischemia and out-of-hospital ventricular fibrillation was suggested by Sharma et al.[10] Of the 15 patients studied who had ventricular fibrillation, 12 had a positive treadmill test result, although none had chest pain. The ischemic changes were associated with an increase in left ventricular pressure and volume. These investigators suggested that the prognosis of patients with silent myocardial ischemia may be worse than that of patients with overt angina pectoris, because painless ischemia may remain unrecognized until a life-threatening cardiac event, such as MI or ventricular fibrillation, occurs.

Silent Ischemia During Daily Activities

My colleagues and I described ischemic changes during everyday activities without accompanying pain in 1973 and 1974.[11–13] In most of the patients, these changes were unprovoked by physical or mental stress and were documented to occur during both day and night. In a subsequent study, many of these patients were found to have severe coronary artery disease on coronary angiography.[14] Silent ischemic episodes during everyday activities were subsequently demonstrated by Shang and Pepine,[15] as well as other workers.[16,17]

The ischemic nature of such episodes of ST depression was provided by Maseri[18] (Italy) and Deanfield et al[19] (England). These groups have shown that silent and symptomatic ischemic episodes are associated with similar hemodynamic alterations and a similar extent of transient myocardial perfusion defects on radionuclide testing. Most investigators agree that about two-thirds of patients with an ischemic response to stress testing have transient ischemic changes during daily activity as well.[20] Approximately 70 to 80% of these episodes are silent.[16,21]

Outcome of Patients with Silent Ischemia in Unstable Angina

The prognostic significance of silent ischemic episodes was evaluated in 70 high-risk patients with unstable angina. Gottlieb et al[22] found that patients who had at least 60 minutes of silent ischemia during 24 hours had a worse prognosis after a 1-month follow-up than those who did not. In these patients, silent ischemia was the best predictor of poor outcome among 15 different variables. A more recent follow-up study of these patients confirmed that the poorer prognosis of the patients with silent ischemia persisted throughout a 2-year period, and infarction and cardiac death were more frequent in the 37 patients than in the 33 patients without silent ischemia.[23] Nademanee et al[24] obtained similar results concerning the prognostic significance of silent ischemia in patients with unstable angina.

TABLE I Cardiac Events During an Average of 24 Months of Follow-Up

	Pts (n)	Events			
		Death	MI	PTCA/CABG	Total
Previous MI with ischemic episodes	76	5	5	13	23
Previous MI, no ischemic episodes	135	5	5	5	15
No previous MI with ischemic episodes	86	3	6	17	26
No previous MI, no ischemic episodes	59	4	2	2	8
Total	356	17	18	37	72

CABG = coronary artery bypass surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Prognostic Significance of Ischemic Episodes During Everyday Activities

In our early study of patients with chronic stable ischemic heart disease, 6- to 12-month follow-up revealed that of the 37 patients who had ischemic episodes during daily activities, 16 had worsening of their anginal state and 7 had pathologic ST-T changes in their ECG at rest. Of the 43 patients without ischemic episodes, deterioration occurred in only 3, and none had electrocardiographic abnormalities at rest.[13]

Recently, we analyzed the data of 356 patients (211 of whom had MI at least 3 months earlier) who had ischemic episodes during activities on Holter monitoring.[25] We included only patients who were active during the day of monitoring and excluded patients with congestive heart failure, those with unstable angina during the previous 3 months of Holter monitoring, or those who had an abnormal ST-T segment at rest. In 76 of the 211 postinfarction patients, we recorded 162 ischemic episodes, 126 (78%) of which were silent. In 59 of the 145 noninfarction patients, we recorded 171 ischemic episodes, 93 (57%) of which were silent.

During a 2-year follow-up period, the patients were examined at least every 6 months. Cardiac death, MI, coronary bypass surgery and balloon angioplasty constituted cardiac events in this study. The Holter monitoring results were not taken into consideration for the decision to submit a patient to 1 of these interventions. Of the 211 patients with previous MI, 76 had ischemic episodes. In this group, 30% had cardiac events compared with only a 9% event rate in those who did not ($p < 0.01$) (Table I). Of the 145 patients without previous infarction, 86 had ischemic episodes; 30% of them had cardiac events compared with 13% in those who did not ($p < 0.025$).

The cardiac event rate in the patients with or without previous infarction was similar in both subgroups; i.e., those with and without ischemic episodes during daily activities. Because high-risk patients (those with signs of heart failure or unstable angina) were exclud-

ed from the study, the expected incidence of mortality and of MI was a priori low. Therefore, it is not surprising that progression of coronary disease during the follow-up period manifested itself mainly by a deterioration in clinical status of patients requiring bypass surgery or balloon angioplasty. These results indicate that patients with coronary artery disease and ischemic episodes, silent or symptomatic, have a worse prognosis than patients without such episodes.

Our results are similar to those reported by DeWood and Rozanski,[26] who reported a worse outcome among the 26 patients with ischemic episodes during Holter monitoring than in 32 patients without. Rocco et al[27] investigated 86 patients with coronary artery disease and found a higher event rate (death, MI, unstable angina, bypass surgery and angioplasty) in patients with ischemic changes during daily activities than in patients without such changes.

Conclusions

Data from published reports indicate that the presence of myocardial ischemia during exercise testing or everyday activities is associated with a higher frequency of subsequent cardiac events, even if not accompanied by pain. Therefore, the management of patients should not only be based on the presence or absence of angina, but also should take into consideration all forms of ischemia—provoked or spontaneous, silent or symptomatic.

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Prognosis in Stable Angina Pectoris and Silent Myocardial Ischemia

MICHAEL E. ASSEY, MD

The results of current investigation suggest that a former clinical standby, namely, the presence or absence of angina, is no longer the principal prognostic factor for determining a patient's risk of cardiac events, including myocardial infarction. In a retrospective analysis, patients with chronic stable angina were compared on the basis of presence or absence of angina during ischemia detected by thallium imaging. Patients were similar in terms of risk factors, clinical characteristics and catheterization data. At 30 months of follow-up, the myocardial infarction rate was 22% in the silent group compared with 4% in the group with angina. Transient asymptomatic ischemia has prognostic value independent of other variables such as exercise stress testing or cardiac catheterization data. Future prognostic studies should be careful to include patient populations with similar characteristics; they also will need to provide protracted follow-up and utilize sensitive and reproducible diagnostic techniques.

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In this era of silent myocardial ischemia, chronic stable angina pectoris is increasingly difficult to define. For the purposes of this review, the syndrome includes patients who are out of the hospital, ambulatory, and stable enough to undergo exercise stress testing.

Current Data

Rabaeus[1] evaluated 150 patients with effort angina who were asymptomatic during a positive exercise treadmill test. All had previous infarction or angiographically documented coronary artery disease. In 45 months of follow-up, 76 of these patients (51%) had a coronary event: 2.5% had unstable angina, 8% had myocardial infarction (MI), 7.5% died suddenly and 33% had to undergo coronary artery bypass grafting.

During a 4-year follow-up, there were 11 sudden cardiac deaths plus 8 other cardiac deaths. Three of these "other" deaths occurred after infarction, 3 occurred after surgery and 2 resulted from late ischemic cardiomyopathy. Thus, the mortality rate totaled 13%, or 3.5%/year in this uncontrolled study.[1]

In the Coronary Artery Surgical Study (CASS), patients exercised and were classified into 4 groups according to the presence or absence of pain and the presence or absence of ST-segment depression. Patients with silent myocardial ischemia had a 1-year survival rate of 76%, which was equivalent to that of patients with angina—whether or not they had ST-segment depression. Seven-year survival rates of patients with silent myocardial ischemia were 86% for those with 1-vessel disease, 73% for those with 2-vessel disease and 57% for those with 3-vessel involvement.[2] Thus, the extent of ischemia—in this case judged angiographically—determined prognosis, independent of angina.

This, of course, had been suggested years before by Cohn et al.[3] In this study, the prognosis for patients with 3-vessel disease and silent ischemia was no better than that of patients with angina and similar coronary anatomy.

Although the study of Amsterdam et al[4] did not specifically look at mortality, it is well documented that in patients with chronic stable angina, the extent of coronary artery disease and left ventricular ejection fraction are valid determinants of prognosis. These determinants were found to be the same in patients with ST-segment depression that occurred without angina or a minute before angina, and in those who had angina without ST-segment depression, or those who had simultaneous ST-segment depression and angina. It is likely that patients with chronic stable angina have a silent element even to their symptomatic ischemic episodes.

From the Division of Cardiology, Medical University of South Carolina College of Medicine, Charleston, South Carolina.

Address for reprints: Michael E. Assey, MD, Division of Cardiology, 816 C5B, Medical University of South Carolina, 171 Ashley Avenue, Charleston, South Carolina 29425

TABLE I Exercise Stress Test Variables*

Variable	Group I—Silent (n = 27)	Group II—Symptomatic (n = 28)	p Value
Exercise duration (sec)	450	345	<0.05
Patients with ≥1 mm ST-segment depression over baseline	11 (41%)	14 (50%)	NS
Maximal heart rate (beats/min)	129	121	NS
Peak systolic blood pressure (mm Hg)	166	152	NS
Peak double product (heart rate × systolic BP)	21,414	18,392	<0.05

* Exercise stress test variables in patients with silent vs symptomatic myocardial infarction. Only 41% of the asymptomatic patients and 50% of the patients with angina had ST-segment depression on electrocardiography; therefore, stress testing that used ST-segment shifts only would have missed the diagnosis in as many as half the patients that were diagnosed as having ischemia based on thallium imaging. (Reprinted with permission by Am J Cardiol 1987;59:498.)

BP = blood pressure; NS = not statistically significantly different.

TABLE II Medical Therapy*

Drug	Group I—Silent (n = 27)	Group II—Symptomatic (n = 28)	p Value
β blockers	18 (67%)	18 (64%)	NS
Calcium channel blockers	11 (41%)	17 (61%)	NS
Nitrates	11 (41%)	22 (82%)	0.01
Aspirin	7 (26%)	11 (39%)	NS
Digoxin	9 (33%)	10 (36%)	NS
Antiarrhythmic therapy	2 (7%)	1 (4%)	NS

* Medical treatment in the 2 groups ranged from β blockade to antiarrhythmic therapy. The only significant difference was in the use of nitrates, which was almost twice as frequent in the symptomatic than in the silent group.

NS = not statistically significantly different.

Falcone et al[5] reported equal survival in 269 symptomatic and 204 asymptomatic patients with similar coronary anatomy and left ventricular ejection fractions. However, patients with silent ischemia were characterized by the following: a longer exercise duration, higher peak double product, more ST-segment depression at peak exercise and exercise-induced ventricular ectopy—a fertile substratum for sudden death in this otherwise chronic stable angina group.

Radionuclide Imaging in Patients with Stable Angina and Silent Myocardial Ischemia

Radionuclide imaging studies have given additional insight into characteristics of patients with silent myocardial ischemia and can enhance detection of those at increased risk for cardiac events.

Reisman et al[6] performed thallium imaging studies in over 1,000 patients who had no previous history of MI or coronary bypass surgery. About 10% of them (160 patients) had hypoperfusion during stress that reached normal levels at rest. Of this group, 83 were asymptomatic and 77 had angina. The cardiac event rate at 1 year was low. However, patients with chronic stable angina may have to be followed longer than 1 year to define the true endpoint, unlike unstable patients who may have a definable endpoint as early as 30 to 60 days. A cardiac event (death, MI, bypass) occurred in 7 (8%) of the asymptomatic and in 14 (18%) of the symptomatic patients. When the events were evaluated in terms of whether these patients had achieved 85% of predicted heart rate, something very important appeared: When unable to reach maximal predicted heart rate, the asymptomatic patients had an event rate similar to that of the symptomatic patients, and the amount of perfusion defect, as judged by number and size of thallium defects, was similar. Therefore, thallium testing identified a high-risk group in an otherwise asymptomatic cohort of patients.

Radionuclear angiography can also be useful when risk-stratifying patients with chronic stable angina. In 131 patients at the National Institutes of Health who underwent cardiac catheterization and exercise testing, there was a very high prevalence of silent ischemia. Patients in this study most likely to have angina were those with left main and 3-vessel disease or a low ejection fraction. All of the deaths occurred in patients who had both an exercise-induced decrease in ejection fraction and ST-segment depression. Dividing these patients into subsets of those with angina and silent myocardial ischemia, the risk of dying with left main disease or with left main and 3-vessel disease was independent of the presence or absence of angina during the test.

TABLE III Cardiac Catheterization Data*

Variable	Group I—Silent (n = 27)	Group II—Symptomatic (n = 28)	p Value
Below normal ejection fraction (<50%)	3 (11%)	4 (14%)	NS
Elevated left ventricular end-diastolic pressure (>12 mm Hg)	12 (44%)	13 (46%)	NS
Left main CAD	1 (4%)	2 (7%)	NS
3-vessel CAD	10 (37%)	12 (43%)	NS
2-vessel CAD	8 (30%)	11 (39%)	NS

* Cardiac catheterization data were not significantly different in the 2 groups. An approximately equal distribution was seen in occurrence of 1-, 2- and 3-vessel disease in the asymptomatic and symptomatic groups. (Reprinted with permission by Am J Cardiol 1987;59:498.)

CAD = coronary artery disease; NS = not statistically significantly different.

Retrospective Findings in Patients with Chronic Stable Angina and Silent Myocardial Ischemia

My colleagues and I performed a retrospective study of 55 patients with angiographically documented coronary artery disease. Group I comprised 27 patients who had transient ischemia without angina during thallium testing; group II comprised 28 patients who had ischemia with angina during the procedure. All of the patients had undergone cardiac catheterization within 6 months of the study; 90% had undergone catheterization within 6 weeks. Patients were followed

for at least 2.5 years to determine the significance of a reversible thallium defect detected during exercise testing that was unrecognized by the patient. Study endpoints were hospitalization for unstable angina, MI and sudden cardiac death.

In the silent group, 41% of patients had ST-segment depression compared with 50% of the symptomatic patients. Thus, if we had just looked at electrocardiographic changes, ischemia would have been detected in only half of our patients. The absence of angina in group I was not due to a submaximal exercise load; all patients were pushed to exhaustion, and the double product was higher in the silent group than in the symptomatic group (Table I).

The clinical characteristics of the 2 groups were similar in terms of known risk factors for coronary atherosclerosis. Drug therapy could not be controlled in this study. However, there was only 1 difference in treatment between the groups: Patients who were symptomatic on the treadmill were taking nitrates more frequently, usually in the form of supplemental sublingual nitroglycerin (Table II). Cardiac catheterization data were also similar in both groups (Table III).

Considering their hemodynamics, these patients should have had a very low complication rate. But at 30 months of follow-up, acute MI had occurred in 6 asymptomatic patients (22%) and in 1 symptomatic patient (4%). There were no unusual findings in the 6 patients who had the infarcts. One of the patients had 1-vessel, 2 had 2-vessel and 3 had 3-vessel disease. In 3 of the asymptomatic patients, infarction terminated in death, for a mortality rate of 11%. None of the patients with angina died. The incidence of hospitalization for unstable angina was 48% in the silent group vs 57% in the group with angina.[8]

We concluded that transient ischemia, identified in this manner, has prognostic value independent of other variables such as standard exercise testing and cardiac catheterization data. The demonstration of exercise-induced silent ischemia may predispose the patient to a higher infarct rate. Certainly, the absence of angina did not impart a better prognosis to these patients.

Considerations for Future Prognostic Studies

In planning future prospective studies on the prognosis of stable angina patients with silent myocardial ischemia, investigators should be careful to select subjects who are free of prognosis-altering medications or interventions, particularly bypass surgery. Our study contained an element of bias because participants were receiving medical treatment. Although we tried to minimize the impact of this by demonstrating equal therapy between groups, a given therapy may not have the same effect in one patient as in another. The study populations should be well defined and homogeneous, with no recent history of MI, and follow-up will have to be prolonged if we are to determine true prognosis. Finally, techniques for detecting silent myocardial ischemia will need to be sensitive and highly reproducible.

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Myocardial Perfusion Imaging for Detection of Silent Myocardial Ischemia

GEORGE A. BELLER, MD

Despite the widespread use of the exercise stress test in diagnosing asymptomatic myocardial ischemia, exercise radionuclide imaging remains useful for detecting silent ischemia in numerous patient populations, including those who are totally asymptomatic, those who have chronic stable angina, those who have recovered from an episode of unstable angina or an uncomplicated myocardial infarction, and those who have undergone angioplasty or received thrombolytic therapy. Studies show that thallium scintigraphy is more sensitive than exercise electrocardiography in detecting ischemia, i.e., in part, because perfusion defects occur more frequently than ST depression and before angina in the ischemic cascade. Thallium-201 scintigraphy can be performed to differentiate a true- from a false-positive exercise electrocardiographic test in patients with exercise-induced ST depression and no angina. The development of technetium-labeled isonitriles may improve the accuracy of myocardial perfusion imaging.

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Exercise radionuclide imaging can help detect silent ischemia in numerous patient populations, including those who are totally asymptomatic, those who have chronic stable angina, and those who have recovered from an episode of unstable angina or an uncomplicated myocardial infarction (MI). Exercise radionuclide imaging is also useful as a follow-up to coronary angioplasty and thrombolytic therapy.

Radionuclide Imaging Versus Exercise Electrocardiography for Detecting Silent Myocardial Ischemia

The rationale for using exercise radionuclide imaging to detect myocardial ischemia is based on the following: (1) perfusion imaging is more sensitive and specific than exercise ST-segment depression in identifying patients with ischemia; (2) patients with high-risk coronary artery disease can be identified by the combination of imaging and exercise electrocardiographic (ECG) stress test variables; and (3) ischemia-induced perfusion abnormalities tend to occur before the onset of angina in patients who are undergoing treadmill testing.

From the University of Virginia School of Medicine, University of Virginia Hospitals, Charlottesville, Virginia.

Address for reprints: George A. Beller, MD, Box 158, University of Virginia Medical Center, Jefferson Park Avenue, Charlottesville, Virginia 22908.

The relative sensitivity and specificity of tests for detecting ischemia in patients with 1-vessel disease and no previous history of MI was undertaken by Port et al.[1] A comparison of exercise electrocardiography, planar and tomographic thallium-201 (Tl-201) and exercise radionuclide angiography demonstrated a sensitivity and specificity of 52% and 72%, respectively, for exercise electrocardiography. The figures were 91% and 83% for planar thallium, 89% and 89% for tomographic thallium, and 65% and 72% for exercise radionuclide angiography. Thus, the exercise radionuclide tests were more sensitive than exercise electrocardiography in detecting ischemia. The perfusion approach in this study demonstrated the optimal balance between sensitivity and specificity for identifying 1-vessel disease.

Another study by Kaul et al[2] similarly found that the prevalence of a Tl-201 defect was approximately 25% more sensitive as an indicator of ischemia than ST-segment depression in patients with 1-vessel disease involving either the left anterior descending, circumflex or right coronary artery.

Canhasi et al[3] compared the accuracy of a markedly positive stress electrocardiogram with that of a high-risk Tl-201 scan in 40 patients with proximal 3-vessel and left main disease. Using the marked positive ECG criteria of ST-segment depression of more than 2 mm, occurring within 6 minutes of the onset of exercise, 15 of these 40 patients were identified as high-risk, a sensitivity of 38%. A high-risk thallium scan, defined as

multiple thallium defects in more than 1 vascular region, increased lung uptake of thallium, or decreased basal uptake or exercise-induced left ventricular dilatation, identified 38 of these 40 patients, yielding a sensitivity of 95%.

One explanation for the enhanced sensitivity of Tl-201 imaging in identifying ischemic and high-risk patients is that it can detect more perfusion defects at a lower rate-pressure product and exercise load compared with prevalence of ST depression with stress testing (Fig. 1). It may take a greater imbalance between oxygen supply and demand, and perhaps more metabolic changes in the heart, before ischemic changes can be detected by the stress electrocardiogram. Coplan et al[4] examined exercise ECG changes in 37 patients with coronary artery disease and Tl-201 redistribution. In the 13 patients who had thallium redistribution and no exercise ST depression, the maximal exercise heart rate was 117 beats/min. In patients who had both ST depression and Tl-201 redistribution, the peak heart rate averaged 132 beats/min.

In another study by Upton et al,[5] a group of 25 patients exercised to an endpoint of either ST depression or angina. These patients all had an abnormal exercise ejection fraction. The stress test was repeated at a lower work level in the same patients. None of the patients had ST expression or angina, but in 18 of the 25 (72%), the ejection fraction was still abnormal or failed to increase by more than 5%, which means that the functional abnormality must have occurred very early during the exercise. The ejection fraction became abnormal in 7 more patients later on. None of the patients had ST depression or angina when the functional disturbance appeared, which correlates very well with the perfusion abnormalities seen in other studies that occurred at an early point during the exercise work load.

Another interesting aspect of the discrepancy between perfusion abnormalities, functional abnormalities, and the exercise electrocardiogram or angina is its possible association with the extent or severity of disease, and not only with the heart rate and work load achieved. Painful episodes of ischemia may be associated with a greater amount of myocardium rendered ischemic than painless episodes.

Thallium-201 Exercise Imaging in the Totally Asymptomatic Patient

In the totally asymptomatic patient, tomographic or planar Tl-201 imaging seems to identify more patients with asymptomatic ischemia than the exercise ECG test alone.[6] This is probably because perfusion imaging is more sensitive than exercise ST depression, particularly at peak exercise heart rates less than 85% of maximal predicted heart rate.

An interesting study involved 130 asymptomatic Air Force pilots who had been referred for catheterization because of coronary risk factors or a positive stress electrocardiogram.[7] Of the 22 who had significant coronary disease, that is, more than 50% stenosis, all had an abnormal Tl-201 scan. Of the 130 patients, 12 were deemed by angiography to have nonsignificant disease, i.e., lesions between 25% and 50%, and of these 12, 8 had abnormal Tl-201 scans. These data suggest that exercise Tl-201 imaging can be the first test performed to identify or confirm presence of silent ischemia in a patient who demonstrates painless ST depression on the exercise electrocardiogram, or who has multiple risk factors and a strong family history of coronary artery disease but a normal exercise electrocardiogram at a suboptimal heart rate response.

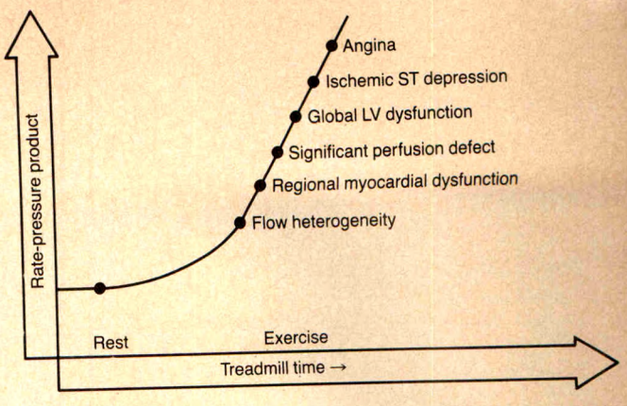

FIGURE 1. A 10% decrease in blood flow is sufficient to cause regional myocardial dysfunction during exercise. This is too small to be detected at low levels of exercise. However, as exercise continues and the rate-pressure product increases, a perfusion defect becomes identifiable by thallium imaging, given significant coronary disease. Perhaps in order for angina to become apparent, the rate-pressure product must get even higher and exercise duration must be longer. LV = left ventricular.

There are asymptomatic patients who have what appears to be a strongly positive exercise electrocardiogram, but no significant abnormalities on thallium scan. Some of these patients may have baseline ECG abnormalities, hypertension, mitral valve prolapse, Wolff-Parkinson-White syndrome, or are receiving digitalis. A Tl-201 scan would help resolve the specificity problems associated with reliance on a single test that has a high false-positive rate in populations with a low pretest likelihood of coronary artery disease. Figure 2 depicts quantitative anterior and 45° left anterior oblique Tl-201 scintigrams in a patient with Wolff-Parkinson-White syndrome and a suspected false-positive ST response to exercise. The scan was entirely normal at a high level of exercise.

Guiney et al[8] studied 35 patients who had ST depression and no angina during exercise stress testing. Patients underwent a Tl-201 stress test before angiography, which identified defects in a group of 11 patients. Subsequent angiography in this group identified 8 patients with significant coronary artery disease and 2 patients with subcritical (<50%) stenoses. Therefore, approximately one-third of the patients actually had silent ischemia, with good correlation between the Tl-201 perfusion scan and the coronary angiogram, and two-thirds (24) of the patients had no defects. In this group, coronary angiography revealed normal coronary arteries in 23 patients and identified

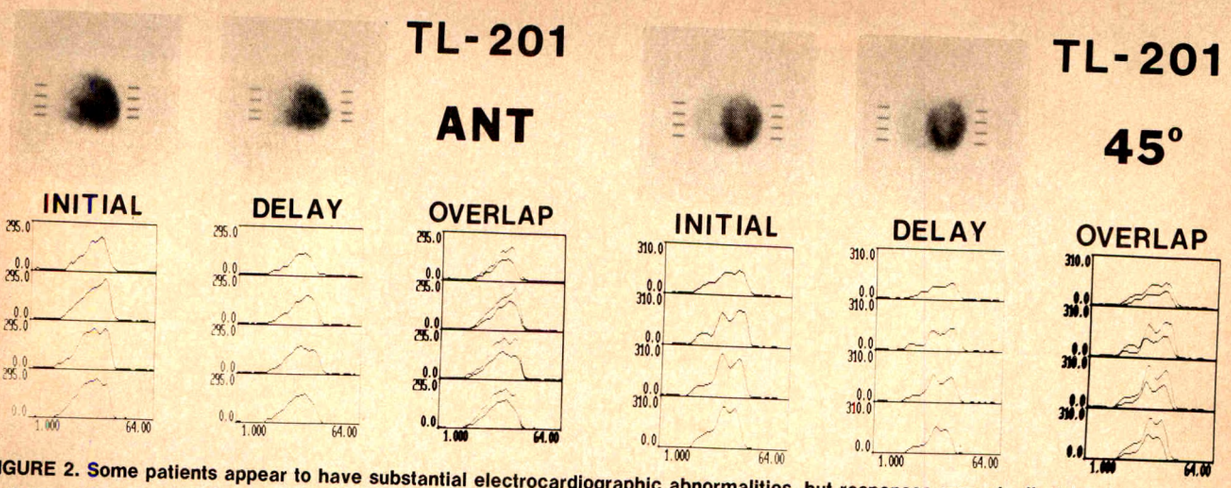

FIGURE 2. Some patients appear to have substantial electrocardiographic abnormalities, but responses are actually false-positive. For instance, this patient had Wolff-Parkinson-White syndrome and a suspected false-positive ST response during exercise testing. The patient's thallium (Tl-201) scan really showed no significant abnormalities by quantitative criteria, and he had false-positive electrocardiographic stress test results. *Left*, anterior (ANT) view scintigram. *Right*, 45° left anterior oblique scintigram. Quantitative count profiles are shown beneath each image and demonstrate uniform thallium-201 uptake and washout from all myocardial segments.

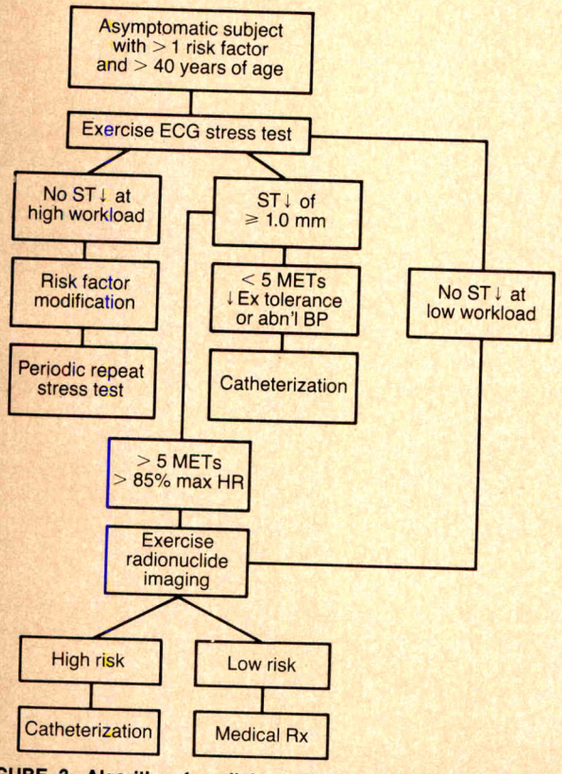

FIGURE 3. Algorithm for clinical management of asymptomatic patients who are older than age 40 years and have more than 1 cardiac risk factor. Patients without ST-segment depression at a high work load are candidates for risk factor reduction and periodic checkup. ST depression that occurs at a low work load calls for cardiac catheterization; when it occurs at a high work load, exercise radionuclide imaging is appropriate. abn'l = abnormal; BP = blood pressure; ECG = electrocardiogram; Ex = exercise; HR = heart rate.

significant 1-vessel disease in 1 patient. These data again illustrate the usefulness of Tl-201 scintigraphy in identifying patients with silent ischemia among those with painless ST-segment depression on a standard exercise ECG stress test.

Approach to Testing the Asymptomatic Patient

Some basic guidelines, derived from clinical experience, can improve the efficiency and accuracy of diagnosing silent myocardial ischemia in the asymptomatic patient (Fig. 3).

In the totally asymptomatic patient who has stress testing for a variety of reasons, such as a strong family history, multiple risk factors, or consideration for a high life-insurance premium, the exercise ECG stress test is cost-effective as the first test to be performed. If the exercise electrocardiogram shows no ST depression or no angina at a very high work load (≥85% or more of maximal heart rate), then risk-factor modification, without repeat testing with Tl-201, would be appropriate because the patient has a low probability of having functionally significant coronary artery disease. A positive ST-segment shift of 1 mm or more that occurs at <5 METs and is associated with either decreased exercise tolerance or an abnormal blood pressure response is probably a true-positive response, since the work load is so low. This test result suggests a high possibility of silent ischemia, and moving directly to cardiac catheterization would be a worthwhile consideration. If there is no ST-segment depression at a low work load, the patient may be demonstrating a false-negative response and therefore is likely to benefit from repeat exercise testing with radionuclide imaging. If the Tl-201 scan suggests high risk, catheterization is appropriate. If the scan indicates low risk, perhaps consistent with 1-vessel right coronary artery disease, medical therapy is a good alternative of

choice. Some patients have ST-segment depression at a very high work load, without accompanying chest pain. This often proves to be a false-positive response; exercise radionuclide imaging can determine whether the patient does, in fact, have ischemia.

Thallium-201 Exercise Imaging After Uncomplicated Myocardial Infarction

Gibson et al[9] evaluated the asymptomatic response in the post-MI setting. Study participants—190 patients who had sustained MI within the past 8 to 10 days—underwent predischarge, submaximal exercise testing to a heart rate of 120 to 130 beats/min, or to 5 METs or less. During testing, 100 patients remained free of angina or ST depression. About half of the patients had Tl-201 redistribution as determined by quantitative scan analysis. In this group, the rate of death or recurrent infarction at about 27 months' follow-up was 24%, compared with 2% in the patients with no ST depression, angina or redistribution (Fig. 4). Therefore, it can be concluded that many of these patients probably did have silent ischemia, evidenced only by Tl-201 redistribution. There was another group of 43 patients who had asymptomatic ST depression on predischarge exercise Tl-201 imaging. In those who also had thallium redistribution, the incidence of recurrent infarction or death (20%) was not substantially different than it was in the group who had no ST depression and Tl-201 redistribution (n = 20). The event rate was higher than observed in patients with ST depression and no associated Tl-201 redistribution (20% vs 9%). Because of this small number of patients, this difference was not statistically significant.

A third group of 47 patients in this post-MI study had angina as an endpoint in the stress test with or without ST depression. Those who also had Tl-201 redistribution (n = 37) had about the same event rate as those without angina and Tl-201 redistribution, irrespective of the presence of ST depression (Fig. 4). Patients with angina and no Tl-201 redistribution had about a 50% lower event rate (10%) than patients with angina and Tl-201 redistribution (24%). Again, because of the relatively low number of patients, this difference was not statistically significant. When development of class III or IV angina in the follow-up period was also considered an event, the difference in event rate in patients with Tl-201 redistribution compared with those without redistribution was statistically significant in all subgroups shown in Figure 4.

Gibson et al[9] made an interesting observation regarding the specificity of the ST response in certain subgroups of post-MI patients. Some patients with circumflex or right coronary infarct-related vessels had significant precordial ST-segment depression in leads V_2 and V_3 on the predischarge exercise test, but no evidence of left anterior descending disease on angiography or Tl-201 redistribution in anterior wall or septal segments. Some had increasing ST-segment elevation in inferoposterior leads in response to exercise, and the precordial ST depression might have represented "reciprocal" changes rather than ischemia. This may account for the group of patients who had silent ST depression without Tl-201 redistribution who had a fairly good prognosis, because they did not manifest ischemia.

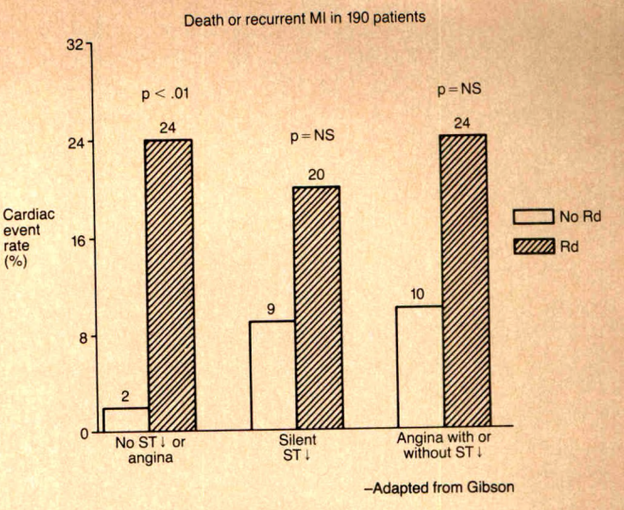

FIGURE 4. Correlation between the cardiac event rate (%) and thallium-perfusion findings in postinfarction patients with no ST depression (↓) or angina (n = 100), silent ST depression (n = 43), or exercise angina with or without ST depression or predischarge exercise testing (n = 47). MI = myocardial infarction; NS = not significant; Rd = thallium-201 redistribution. (Adapted from Gibson et al.[9])

The results of this study suggest that silent ischemia occurs often after uncomplicated MI and identifies a subset of patients at a higher risk for recurrent infarction and death. Tl-201 scintigraphy improves both sensitivity and specificity for identifying these high-risk patients.

Limitations of Thallium Imaging

As with so many diagnostic tools, Tl-201 imaging does have some limitations. Because of its low-energy emission, there are many attenuation artifacts that increase the false-positive rate. The false-positive rate is also high in patients with left bundle branch block and patients who have exaggerated apical thinning. Left circumflex and milder stenoses are not as easily detected as left anterior descending and right coronary lesions, or lesions of >80% narrowing. Tl-201 has a long half-life, is expensive, and requires quantitation of uptake and washout for optimal use.

Future Advances in Imaging Technology

A new agent—a technetium-labeled isonitrile, 2-methoxyisobutyl isonitrile (MIBI)—also is taken up by the myocardium in proportion to blood flow. The scintigraphic images it provides in animals and humans is comparable to that achieved with Tl-201. It may give better resolution of the posterior wall, particularly in a 70° projection, and in preliminary studies there ap-

pears to be a good correlation between abnormal perfusion and abnormal wall motion. Because this is a technetium-labeled perfusion agent, images can be easily gated. Furthermore, MIBI does not redistribute, which means that images can be obtained as they would appear immediately after exercise—even after a delay. This is because the isonitrile enters the myocardium passively through the sarcolemmal membrane, and has a subsequent very slow washout.

In a preliminary study comparing the Tl-201 scan with the technetium-99m MIBI scan in the same patient, there was good correlation with segments interpreted as normal, showing ischemia or scarring with some discordance on either side.[10] Early studies, suggesting that MIBI imaging is as good as Tl-201 scintigraphy in detecting coronary artery disease, are encouraging.[11]

Positron emission computed tomography also holds promise for imaging regional myocardial blood flow using rubidium-82 as the perfusion agent. Preliminary clinical studies suggest a high sensitivity and specificity for coronary artery disease detection.

In summary, myocardial perfusion imaging is a useful technique, particularly for identifying patients with silent ischemia. Patients who have Tl-201 redistribution without pain appear to have a worse prognosis than patients with no scintigraphic evidence of ischemia. In post-MI patients, Tl-201 redistribution is also more specific than ST depression for identifying those with residual ischemia. Newer technetium-99m-labeled perfusion agents and positron imaging with $^{82}Rb^{+}$ appear promising for enhancing the diagnostic and prognostic capabilities of exercise radionuclide imaging.

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Discussion III

Dr. Assey (*Charleston, South Carolina*): I have 2 questions concerning Dr. Stern's prognostic update in patients with silent myocardial ischemia. Were study participants on routine medical therapy, and if so, was that controlled for in the overall end results? Secondly, was the decision to proceed to angioplasty based on Holter monitoring data?

Dr. Stern (*Jerusalem, Israel*): To answer your first question, the patients were on routine medical therapy. We could not find any significant difference between therapy in patients who had ischemic episodes vs those who did not. The second question is very relative. The results of Holter monitoring were not taken into consideration when deciding whether to send the patient for angioplasty or surgery.

Dr. Horwitz (*Denver, Colorado*): I would like to comment on the use of exercise testing compared with Holter monitoring for determining prognosis. Overwhelmingly, the most reliable prognostic evidence from an exercise test is exercise capacity. The detection of ischemia, whether by thallium or electrocardiogram, is much less certain. I think most of us use exercise testing not just to see whether it is positive. Rather, if a test is positive at a high exercise load, it concerns us a lot less if the exercise test is positive by ST-segment shift or radionuclide angiography at a low level of exercise. A positive Holter monitor during everyday activities is, in a sense, detecting ischemia at a low exercise load. When comparing this with whether there is a positive exercise test, you are comparing these people with some who may only get ischemia at an extraordinarily high load. In terms of prognosis, it is more valuable to divide positive exercise tests between those who are positive at a high load only and those who are positive at a relatively low load. Those people seem to have a very bad prognosis, whether or not they have angina, either because they have a large area of ischemia, which suddenly impairs performance, or because there is a lot of underlying fixed disease. I don't think it is nearly as valuable to compare monitoring data with a positive test, without regard to the work level at which the positive response occurs.

Dr. Cohn (*Stony Brook, New York*): Dr. Stern, do you want to respond in terms of the breakdown of your patients who had a positive exercise test?

Dr. Stern: I fully agree that so far, with Holter monitoring, we are speaking about a "yes" or "no" situation. Is the patient having ischemic episodes or not? The situation with exercise testing is currently very similar. Most of the exercise tests are classified as either positive or negative. But I agree that the low-load positive exercise test may have a completely different prognostic significance than a high-load positive exercise test. We really should consider our results according to the degree of work during the exercise test.

Dr. Friesinger (*Nashville, Tennessee*): To extend that, the increase in myocardial oxygen demand is much less during Holter monitoring than during exercise testing, suggesting a different pathophysiologic mechanism for ischemia, namely, that the vascular reactivity of the bed differs from that during exercise. One way this has been evaluated is by examining the duration of ST-segment depression during a 24-hour period. I was wondering if anyone has examined the duration of ischemia during a 24-hour period, to check the possibility that the bed is more reactive, that coronary tone has changed, and that these patients are in a less stable phase of their ischemic disease.

Dr. Stern: I agree that we should find out which is the most significant determinant of ischemia on Holter monitoring. Is it the duration of this ischemic period? Is it the heart rate at which ischemia appears? Is it the degree of ST depression (1 mm vs 2 mm or 3 mm)? I have to agree that we do not have an answer for that yet. We are trying to look into it now.

Dr. Assey: In our study of stable angina, we didn't simultaneously look at ambulatory electrocardiographic monitoring in patients who were exercised. So, I cannot answer the question. Although the potential for different ischemic mechanisms is undeniable, the role of sympathetically mediated changes in vasomotor tone during exercise is also a complicating factor.

Dr. Amsterdam (*Davis, California*): We also have to consider that ischemia during relatively low heart rates associated with everyday activities may still relate to increased oxygen demand, because blood pressure is not usually measured out of hospital. While there can be increases in coronary tone, it is still possible that demand is a component, i.e., blood pressure may be high. Those are difficult data to get, even with an ambulatory blood pressure monitor, because there is a limit to how frequently pressure measurements can be obtained.

Dr. Deanfield (*London, England*): Investigators at Hammersmith have examined amulatory blood pressure with a continuous intra-arterial recording (ST-segment depression on frequency-modulated boxes). Unlike the heart rate, blood pressure does not rise before the onset of ST-segment depression during daily life. Still, that does not negate the potential relevancy of changes in myocardial oxygen consumption to the genesis of ischemia out of hospital.

Dr. Hollenberg (*San Francisco, California*): I could add that during intraoperative monitoring, which gives continuous blood pressure and transesophageal echocardiographic recordings, most of the ischemic episodes that we see are not associated with changes in heart rate/blood pressure. Al-

most inevitably they are associated with significant changes in regional wall or global dysfunction, as seen on transesophageal echo. We have also seen marked deterioration of left ventricular function, as evidenced by a significantly decreased ejection fraction, associated with an obviously ischemic episode—that was not associated with ST-segment changes on 12-lead monitor during the operation, but with a substantial increase in R-wave height. Now, we probably could discuss for an hour what changes in R-wave values mean electrocardiographically. There is no question that, in the operating room, there is a correlation between changes in left ventricular function and R-wave changes not associated with significant ST-segment changes. There may be other markers of the ischemic event than pure ST-segment changes alone. I would like to make one other comment, and I am glad that the exercise tests were so amply defended by Dr. Horwitz. I think we are now comparing qualitative changes in the electrocardiogram with qualitative changes by thallium imaging. What we have to progress to is quantitation of the exercise test both electrocardiographically and by thallium. Presently, when we talk about a thallium defect, we make very little discrimination whether this defect is provoked after 3 or after 15 minutes of exercise. We talk about a reversible defect, or a nonreversible defect, and we almost never mention what level of exercise is necessary to induce it, or what are the hemodynamic parameters that are necessary to elicit such nonhomogeneous perfusion. I would make a plea to start looking at it in a more sophisticated fashion. We classify high-risk patients as those needing more than 2 mm ST depression, and yet we totally ignore the QRS amplitude in the monitored lead. Is the R wave at rest 8 mm or 30 mm tall? We have shown that you have to relate the ST-segment depression to the R wave that is monitored.[1] A 0.7 mm depression is a small QRS complex that occurs at 3 minutes of exercise may be highly significant and may represent a strong positive response, whereas a 3 mm depression that is elicited at 13 or 14 minutes of exercise may be normal. So, I think we are being very simplistic in the kind of qualitative comparison we are making between the exercise thallium and the exercise electrocardiogram as diagnostic tools. We are presently able to quantify electrocardiographic responses by more sophisticated methods. Further, we have attempted to quantify thallium defects and relate them to the work load necessary to elicit a certain volume of myocardium that exhibits nonhomogeneous flow. I would like to see more discussion of these quantitative aspects, and not whether thallium is better than the electrocardiographic interpretation that has been used for 40 years and that we really have not improved upon.

Dr. Silber (*Birmingham, Alabama*): Our discussion should not go in the direction of comparing exercise radionuclide studies with exercise electrocardiographic studies. There is so much information showing that exercise radionuclide studies are more sensitive and specific than exercise electrocardiography. The point in comparing radionuclide techniques with electrocardiograms is that the ST segment has 1 major advantage: the possibility of ambulatory monitoring. The key question is, what is the difference between ambulatory ST-segment monitoring and the exercise test? If we have a middle-aged asymptomatic patient with more than 1 risk factor, where is the place for exercise testing and for Holter monitoring? Should we do both, or can we just rely on one of these tests? I think we need more data to determine if we are measuring 2 different things.

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Identification of High-Risk Patients with Silent Myocardial Ischemia After Percutaneous Transluminal Coronary Angioplasty by Multilead Monitoring

MITCHELL KRUCOFF, MD

Quantification of total ischemic burden can be improved by use of microprocessor-driven, multichannel, digital, ST-monitoring devices. ST deviation recorded during angioplasty provides a patient-specific template for identification of patients at increased risk for coronary events after angiographically successful dilation. In patients with ST-segment elevation, evidence of these ST "fingerprint" patterns are associated with elevated risk for coronary events in the postangioplasty period. Such risk is not seen in patients with ST-segment depression or with no ST changes. The increased monitoring capability afforded with digitized 3- or 12-lead monitoring creates new criteria for what constitutes accurate determination of total ischemic burden.

(Am J Cardiol 1988;61:29F-34F)

In the quantitation of ischemic burden, there is no more rapidly emerging technology than the addition of microprocessor capability to electrocardiography/ST-segment monitoring. This certainly heralds a new era of diagnostic capability that may improve our ability to monitor disease activity and identify high-risk patients.

Early ST-Segment Monitoring: More Leads to More Definition

In its early stages, ST monitoring was impeded by a high rate of false-positive diagnoses resulting from patient selection and the equipment used. In the 1970s, Wolf et al,[1] using a single-channel Holter recorder with improved frequency response, were able to gather accurate information, validated against simultaneous exercise recordings. They later applied a dual-channel recorder that increased the sensitivity of ischemia detection.[2] Simultaneously, in the 1970s, Selwyn et al[3] were placing multiple leads over the precordium during exercise and mapping out precordial zones of ST activity, which, in an exercise context, was consolidated to 2 zones in a V_2–V_3 area and an inferolateral V_5-like area. Most of the currently reported Holter data from patients with silent ischemia use lead placements extrapolated from their technique and results.

There has been, however, another use of multiple-lead acquisitions in earlier studies, not on exercise tests or Holter monitors, but from 12-lead electrocardiograms in patients with coronary occlusion and myocardial infarction. For several decades, anterior, posterior, inferior and lateral myocardial infarction has been described on the basis of 12-lead electrocardiographic patterns. Unlike the poor correlation found between coronary anatomy and the precordial zones during exercise on a treadmill, precordial patterns of ST elevation or injury current usually correspond well with coronary anatomy, identifying the epicardial vessel involved. This has been emphasized by work like Maroko et al[4], using multilead ST maps to define not only the location of myocardial injury but also a zone of risk that is proportional to the jeopardized myocardium in the setting of coronary occlusion. In addition, there is a considerable number of studies in the literature, evaluating not only areas of injury but also areas of reciprocal ST changes. In the setting of myocardial infarction, reciprocal changes seem to define a patient population with a poorer clinical prognosis.[5]

Thus, multilead recordings provide important anatomic and prognostic information, as well as improved episode detection when used for evaluation of total ischemic burden. Microprocessor technology makes

From the Division of Cardiology, Georgetown University Hospital, Washington, D.C.

Address for reprints: Mitchell Krucoff, MD, Division of Cardiology, Georgetown University Hospital, 3800 Reservoir Road, NW, Washington, D.C. 20007.

analysis of multilead data a reality in current commercially available devices.

Quantitating Total Ischemic Burden

Many approaches to ST monitoring for quantitating total ischemic burden involve examining arbitrary parameters, such as the number of episodes during a recording period, the duration of each episode (individually and together with all episodes), the severity or actual ST deviation of each episode, or the peak ST deviation over a recording period. There is also a range of technical considerations, such as selecting patients who have known coronary disease to try to eliminate false-positive diagnoses, record/playback electronics, low-frequency response, phase-shift, the duration of recording, the placement of leads, and the number of leads needed to accurately quantitate ischemic activity.

Much of the mapping work that has been done has focused on identifying a precordial central zone of ischemia, i.e., the area of peak severity that would then be an ideal place for an electrode to record all of the episodes as well as the maximal ST deviation. This is assumed by most investigators to also be the position that will show the longest duration of abnormal activity. Numerous factors may modify the precordial zone of activity, including the development of collaterals to the vessel, changes in medications, or the presence of multiple vessels with stenoses.

Computerized Ischemia Monitoring: Method

Two monitoring devices are used in our laboratory (Georgetown Ischemia Monitoring Laboratory): a 3-channel Holter (Scole Alta II), analyzed on a fully digitizing playback computer (Marquette 8000) and a 12-lead real-time portable programmable ST monitor (Mortara EL-I).

Holter recordings are continuous in 3 standard bipolar vectors: leads V_2, V_5 and aVF. Digital playback analysis is performed only on normally conducted beats, with a mean ST level generated every 10 seconds. This high-resolution analysis allows detection and quantitation of even very brief ischemic episodes, such as balloon occlusions during percutaneous transluminal coronary angioplasty (PTCA) (Fig. 1). Low-frequency response and phase shift of this system have been previously validated with a programmable electrocardiographic/ST calibration signal throughout.[6]

The 12-lead ST monitor acquires standard electrocardiograms every 30 seconds. ST level at J + 60 ms in every lead is instantly compared with a baseline electrocardiographic template. The device can be programmed to alarm if ST deviation is detected on 2 electrocardiograms in a row over a 60-second period.

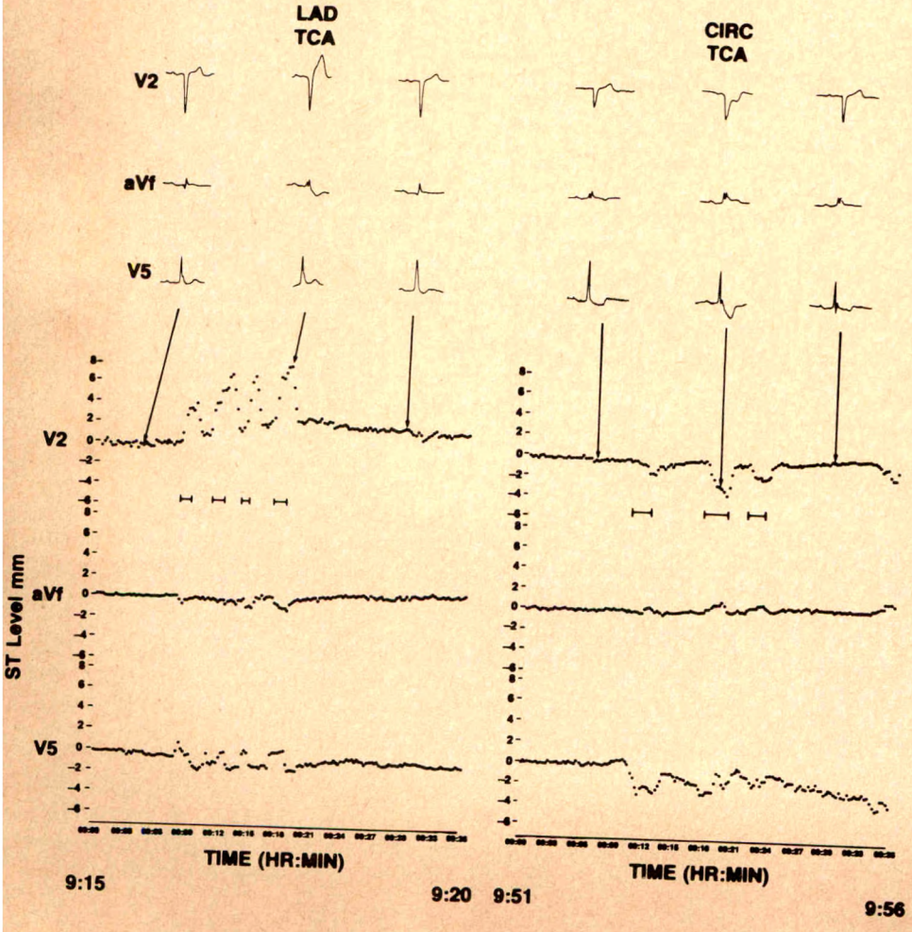
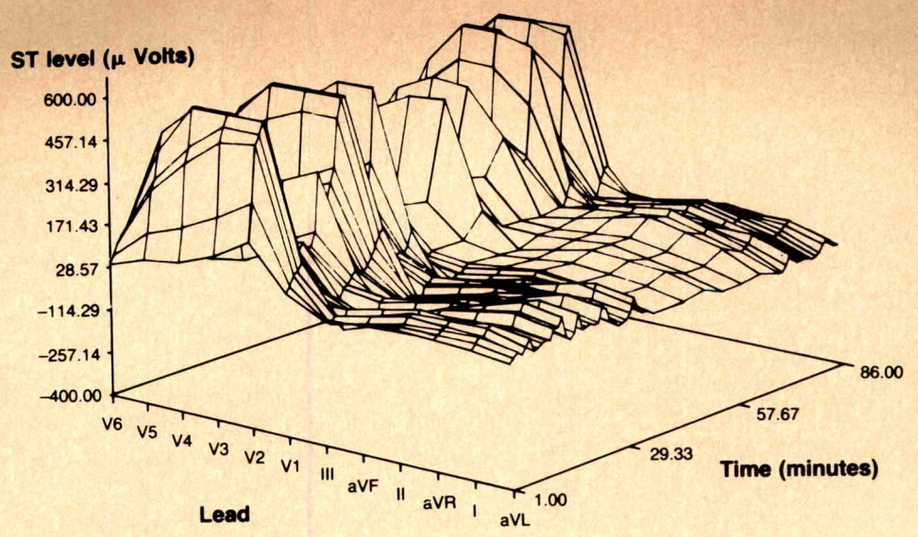


FIGURE 1. High-resolution 3-channel ST-segment trend during percutaneous transluminal coronary angioplasty (TCA) of the left anterior descending artery (LAD) and circumflex (CIRC) arteries in the same patient. *Horizontal bars* show balloon inflations in each artery. Discrete reproducible patterns of anterolateral ST elevation with some reciprocal inferior ST depression are seen during occlusion of left anterior descending artery, compared with inferior ST elevation with anterolateral ST depression during circumflex occlusion in the same patient.



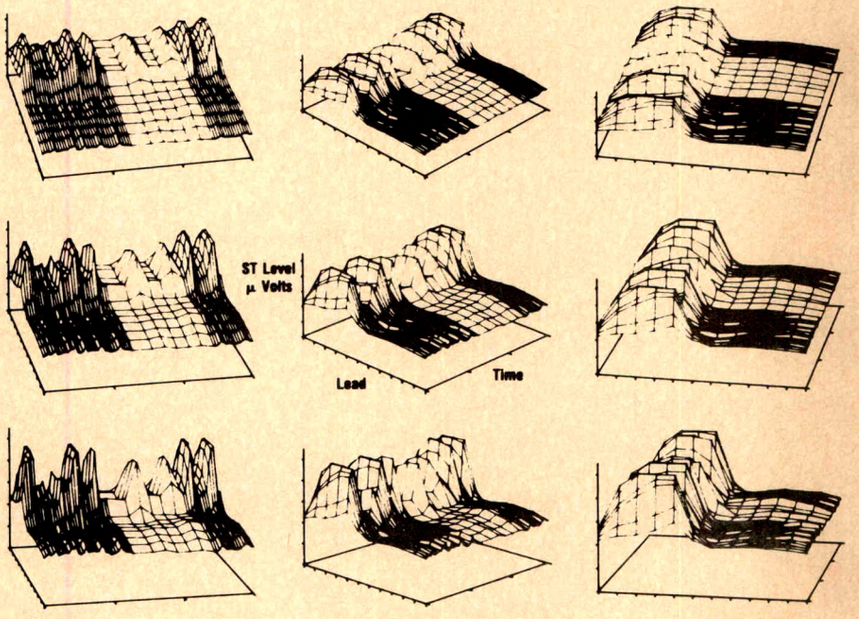
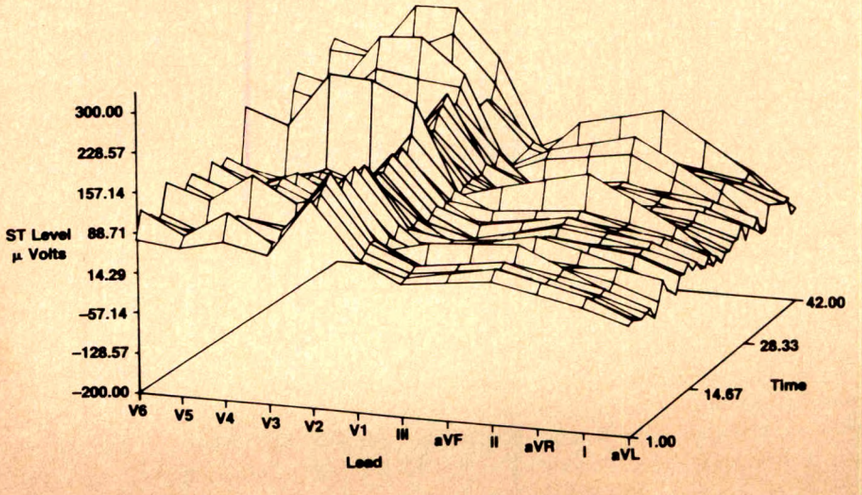


FIGURE 2. High-resolution 12-lead acquisition during percutaneous transluminal coronary angioplasty of a left anterior descending/diagonal branch bifurcation lesion, showing full precordial extent of anterolateral ST elevation, as well as reciprocal inferior ST depression (*top*). Spatial rotations of recording (*top*) show duration of each of 9 dilatations (*left*) as well as reproducibility of ST fingerprint for occlusion at that site (*middle*). Coronary care unit recording from the same patient, showing recurrence of the same ST fingerprint during spontaneous episodes of ischemia (*bottom*).



Electrocardiograms are digitally stored and may be down-loaded to an IBM-PC for further analysis (Fig. 2). Low-frequency response of this system meets American Heart Association standards for an electrocardiographic chart.

Computerized Ischemia Monitoring: Results

At the Georgetown Ischemia Monitoring Laboratory data base, over 11,000 hours of monitoring have been completed in 560 patients during and after PTCA. That includes almost 2,600 transient coronary occlusions during angioplasty, as well as 23 spontaneous myocardial infarctions after angioplasty.

Each patient averaged 4 to 5 occlusions lasting more than 60 seconds in duration. The population distribution was fairly typical, with 49% left anterior descending (LAD), 32% right coronary artery, and 19% left circumflex occlusions. About one-third of the patients had visible collateral flow and about two-thirds had multivessel disease.

The average recording period after PTCA was 19.6 hours. Some ST deviation was recorded during PTCA in 79% of patients. Most of the other 21% of patients had collaterals visible to the target vessel. Of those who had ST deviation, 86% had injury current recorded in 1 of the standard placement leads; the other 14% had ST depression only. Only ST depression was seen most often with circumflex lesions or with collateralized vessels, or both. About one-fourth (25%) of patients showing ST elevation had involvement in more than 2 leads. About 20% had only ST elevation, and nearly 50% had some combination of ST elevation and reciprocal ST depression.[7]

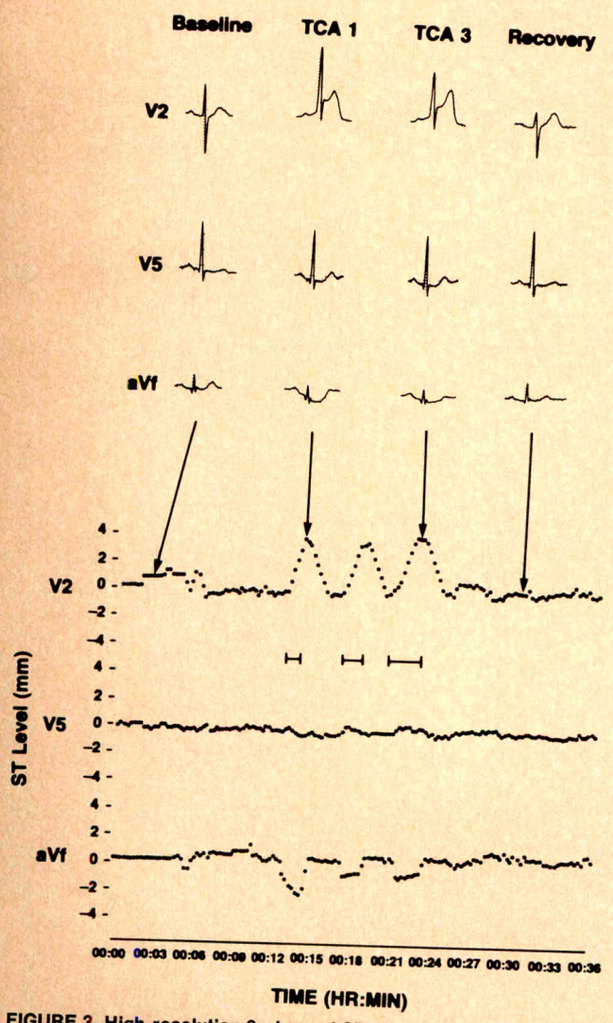


FIGURE 3. High-resolution 3-channel ST trend during percutaneous transluminal coronary angioplasty (TCA) of lesion in the left anterior descending artery showing anterior ST elevation with reciprocal inferior ST depression. Monitoring of lead V_5 in this patient would have completely missed all 3 left anterior descending occlusions. (Reprinted with permission from Springer-Verlag, Darmstadt.)

Detection of ST Changes in Different Leads: How Many Leads Are Enough?

The detection rate of ST-segment changes in our patients varied according to lead analyzed and site of obstruction. With occlusion of the LAD, approximately 95% of patients had ST deviation (elevation or depression) in V_2, 65% had some change in V_5 and 70% had a change manifested in aVF. Occlusion in the right coronary artery was associated with 78% incidence of ST change in V_2, 68% had changes in V_5 and 86% had aVF changes. In the circumflex artery, 90% of patients had some change anteriorly, 70% had ST elevation or depression in V_5 and 72% had changes in aVF.

Conversely, we see the potential for completely missing ST-segment changes during arterial occlusions (Fig. 3). With LAD obstruction, V_5 is the least sensitive lead. With blockage of the right coronary artery, about one-third of patients have no activity at all in the V_2 or V_5 locations. In a circumflex obstruction, V_5 and aVF each fail to detect any ST deviation in about one-third of patients.

Single-lead monitoring could not only miss ischemic episodes entirely but also would fail to show the full scope of ST changes. If only V_2 was monitored over our entire population, ST elevation would be missed in about one-third of the events and ST depression would be missed in approximately 40% of the coronary occlusions. With use of V_5 alone, ST elevation or ST depression, or both, are missed in 81% of occlusions. With aVF alone, the ranges are similar to those with V_5, missing ST elevation in about 50% of the cases and ST depression in about 30%.

Two-channel monitoring improves both the detection and the definition of ischemic episodes. Combining V_2 and V_5 records ST changes completely in 59% of patients, misses some ST elevation in 17% and misses ST depression in 23%. The combination of V_2 and aVF gives the best yield for complete definition (87%); 5% of the time it misses ST elevation and 7% of the time ST depression is missed. Using V_5 and aVF together completely defined ST episodes in 45% of patients. In 32% ST elevation was missed and in 21% ST depression was missed.

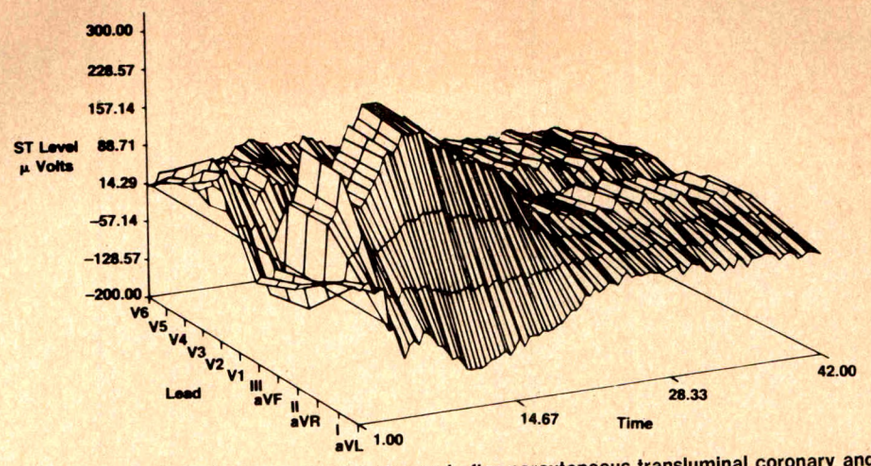


FIGURE 4. High-resolution 12-lead acquisition in a patient during and after percutaneous transluminal coronary angioplasty in the right coronary artery. Initial electrocardiograms show ST elevation in anterior leads from early repolarization at baseline. Inferior ST elevation with reciprocal anterior ST depression is then seen during percutaneous transluminal coronary angioplasty. Despite excellent angiographic results, ST fingerprint recurs during 6-hour-long inferior myocardial infarction. The patient had no symptoms at all. (Reprinted with permission from Springer-Verlag, Darmstadt.)

Our data thus illustrate how incompletely single- and dual-channel monitoring would characterize transient ischemic episodes. Even if nonquantitative episode detection was the goal, our data show that the lead pair V_2 and aVF perform best for detection of transient coronary occlusion, whereas previous work has indicated that V_5 performs best for episodes of subendocardial ischemia. Thus, comprehensive quantitation of total ischemic burden requires monitoring of a minimum of 3 lead locations.

Quantitative ST Monitoring: Prognosis After Percutaneous Transluminal Coronary Angioplasty

Although accurate multilead quantification of total ischemic burden is technically feasible, the prognostic significance requires definition. We have examined ST-segment episodes in patients after successful PTCA to see if ST-segment deviation can identify patients who are at high risk for coronary events while still in the coronary care unit. Of our first 282 patients after successful PTCA, 65 (23%) had some ST deviation during the 19 hours of ST monitoring after the procedure. In this group, 18 patients had myocardial infarction, 5 patients had bypass and 2 died. Patients who had no ST deviation had no coronary events after angioplasty.[8]

Of the 65 patients with ST episodes after PTCA, 40% had no symptoms at all during ischemic episodes (Fig. 4), 22% had a mixture of silent and symptomatic episodes, and 25% had an "early warning period" of >15 minutes in which ST segments were markedly abnormal before symptoms appeared. In a hospital setting, this time window is adequate for intervention. Thus, transient ischemia after PTCA was silent in 84% of the patients who had any ischemia early after angioplasty.

Importance of Multilead Recording: The ST Fingerprint

Whereas patients with detectable ST episodes had a worse prognosis than patients with no ST episodes after PTCA, multilead recording allowed further definition of such episodes, establishing a hierarchy of higher and lower risk patterns. By recording during PTCA, individualized ST patterns during balloon inflation were established as templates or ST fingerprints of coronary occlusion at that site.[7]

Among patients with ST episodes after PTCA, 8% of patients with only ST depression had myocardial infarction, compared with 60% of patients with any ST elevation. Of patients with ST elevation, all of those with late episodes in the same pattern as that seen during PTCA, i.e., those whose ST fingerprint matched that taken during PTCA, had myocardial infarction or urgent coronary artery bypass graft.[8]

Thus, patients with ST episodes were at higher risk than those with no episodes, patients with ST elevation were at higher risk than those with ST depression, and patients with ST elevation matching the multilead ST fingerprint seen during PTCA were at higher risk of myocardial infarction, urgent bypass or death.

Conclusion

New technologies with improved electronics and data-processing capability have made real-time multilead continuous ST-segment monitoring feasible for quantitating total ischemic burden in patients in critical-care settings. When added to the widely used symptomatic and rhythm monitoring performed in the coronary care unit in patients after successful PTCA and using multilead ST fingerprint patterns recorded during PTCA in each patient, ST-segment monitoring provided a hierarchy of patterns for subgrouping pa

tients at risk of myocardial infarction in the hospital. Patients with any ST episodes were at greater risk than those with no ST episodes; patients with any ST elevation were at greater risk than those with only ST depression; and patients with ST elevation in a pattern matching the ST fingerprint obtained during PTCA were at the highest risk of all.

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Discussion IV

Dr. Cohn (*Stony Brook, New York*): I would like to entertain questions and comments pertaining to Dr. Krucoff's presentation.

Dr. Cabin (*New Haven, Connecticut*): Dr. Krucoff, did you evaluate prognostic data in relation to other prognostic variables, such as residual gradient stenoses or dissections?

Dr. Krucoff (*Washington, D.C.*): We didn't have gradient data because we don't record them with the equipment we use. Our patients were those whose dissection and other high-risk variables did not clearly identify. All had apparently successful angioplasty, had left the catheterization laboratory, and were in the coronary care unit. In that subgroup, the presence of intimal dissection, especially, did not identify a lot of these patients. All complications were in-hospital.

Dr. Cabin: Have you examined long-term outcome?

Dr. Krucoff: Not yet.

Dr. Friesinger (*Nashville, Tennessee*): Dr. Krucoff, how available is this technology, especially the data processing?

Dr. Krucoff: The Holter system that we use—a 3-channel recorder—is available from Scole Engineering in Los Angeles. The data processing on the Holter is a standard, commercially available Marquette 8000 playback. Their commercial software will now handle 3 simultaneous leads. It is no more or less difficult than playing back any other Holter tape. Obviously, the same considerations apply as in analyzing 2-channel readout—artifact has to be edited, aberrantly conducted beats have to be deleted, all of that. The 12-lead Mortara EL-I is a commercially available device. The software playback to generate the 3-dimensional graphic displays will probably be a part of that package in the coming year. Currently, the device gives a real time, full-disclosure output; it has its own little minireport that it will print out.

Dr. Sharma (*Little Rock, Arkansas*): My colleagues and I have been monitoring epicardial leads with simultaneous multiple surface leads in patients during percutaneous transluminal coronary angioplasty. This epicardial electrode is the bare 0.5 mm tip of the otherwise Teflon®-coated steerable guidewire. Thus, we have a unipolar epicardial electrode with which to monitor iatrogenic myocardial ischemia during angioplasty. We have used this technique to analyze 188 patients undergoing percutaneous transluminal coronary angioplasty and found it to be highly sensitive. We find virtually all patients have epicardial evidence of myocardial ischemia associated with balloon inflation. However, only 20% of patients reflect the epicardial evidence of ischemia on the surface precordial leads. What we and other investigators (Friedman et al) are suggesting is that many episodes of regional myocardial ischemia may remain undetected when standard surface electrocardiography techniques are used. Can you comment on that?

Dr. Krucoff: Yes. I think that epicardial recording, as has been reported, is a very elegant technique. However, we can go one step beyond the electrocardiogram in the catheterization laboratory. Echocardiography data have been reported, with an even superior detection of ischemic ventricular wall motion abnormalities. The problem is with the practicality of this in the clinical world and in the patient who goes to the coronary care unit. You can't leave a guidewire in an epicardial artery, and the patient can't drag an echo machine as he or she goes around.

Dr. Sharma: What we have found in about 16% of patients is an ST-T alternation, with one being elevated and one being depressed. How would your mapping handle this?

Dr. Krucoff: We've seen this, but not in actual up-down. We've seen it go from 5 to 4, to 5 to 4.

Dr. Sharma: We have seen just the reverse.

Dr. Krucoff: That's a new one on me, at least in this population. Our devices would handle this by taking a mathematical average of all normally conducted beats recorded at the highest resolution, which is 10 seconds. So, if there is an up-down, up-down, it will just take the mean of that 10-second period. In terms of our detection rate, if you subtract our patients with collaterals, we see ST deviation in 91% of patients. Around 10% or 11% is ST depression only, and the other 80% is ST elevation. Some of that clearly has to do, I think, with circumflex locations; we're still following old recording techniques. The high lateral area is still elusive for standard lead placements, as are the true apex and distal left anterior descending distributions.

Dr. Silber (*Birmingham, Alabama*): The results are convincing that 2 leads are better than 1, but are 3 leads much better than 2? How many percent were missed by using 2 leads compared with 3?

Dr. Krucoff: In the setting of coronary artery occlusion, using aVF and V_2, you would see nothing in 1% of the patients; in 99%, you would detect a "yes-no." The trouble is, if you used an aVF and V_2 for people on treadmill, you would miss significantly more than that because V_5 is actually the most active area. And, in V_5, you entirely miss almost 30% of coronary occlusions.

Dr. Silber: But, in your model you only miss 1% by using 2 leads.

Dr. Krucoff: With aVF and V_2. So, again, those are not the same 2 channels that you'd probably want to use in ambulatory patients.

Clinical Implications of Coronary Arteriographic Findings Soon After Non-Q-Wave Acute Myocardial Infarction

MARCUS A. DeWOOD, MD

A significant incidence of death and myocardial infarction after non-Q-wave infarction belies the earlier impression that it is less serious than Q-wave infarction. Coronary angiography in the early stages after non-Q-wave infarction shows a progressive increase in the number of totally occluded vessels. This is paralleled by an increase in number of collateral vessels. Thrombus also becomes increasingly prevalent over the week after non-Q-wave infarction, and plays a role in 30 to 40% of infarctions.

(Am J Cardiol 1988;61:36F–38F)

Although non-Q-wave myocardial infarction (MI) was orignially considered to be less serious than Q-wave infarction, subsequent investigations have indicted that the incidence of death and recurrent MI is as great as that associated with Q-wave infarcts.[1,2] My co-workers and I were interested in defining coronary arteriographic findings early after non-Q-wave MI. The goals of this study were to determine the presence of complete coronary occlusion in the infarct-related vessel, as well as to determine frequency of coronary collaterals.

Study Design

We tried to define the frequency of coronary occlusion within a week of the peak symptoms in patients who had sustained non-Q-wave MI. We also attempted to determine the frequency of coronary collaterals in the same population.

The criteria for non-Q-wave MI were standard: (1) chest pain, (2) ST- and T-wave abnormalities without evolution of new Q waves, and (3) abnormal MB-creatine kinase activity.

The investigation was conducted as a combined retrospective and prospective study over a 10-year period. A total of 341 patients were studied: 161 during the retrospective period from 1974 to 1979, and 180 during the prospective period from 1980 to 1984.

From the Deaconess Medical Center, Sacred Heart Medical Center, Spokane, Washington.

Address for reprints: Marcus A. DeWood, MD, Deaconess Medical Center, 800 West Fifth Avenue, Spokane, Washington 99204.

Of those 341 patients, 192 were studied within 24 hours of peak symptoms, while 94 underwent investigation in the 24- to 72-hour time period, and 55 were studied after 3 days but within 1 week of non-Q-wave MI. The clinical and laboratory characteristics of the various groups were similar. We were surprised that many patients (approximately 50% in each group) had anterior ST-T changes, and yet lesions were thought to be active elsewhere in the coronary tree—not indicating involvement of the left anterior descending artery. This may have been due to distant ischemia. All patients underwent coronary arteriography and left ventriculography within 1 week of peak symptoms.

Results

None of the patients had normal results on coronary arteriography. Serious left main disease (over 50% obstruction) was present in 30 of the 341 (9%) patients. Although a few patients had filling defects, most patients simply had tight coronary stenosis (Fig. 1). Most of the patients also had coronary collaterals, probably protecting them (at least partially) from major ST-segment elevation associated with a current of injury (Fig. 2).

Essentially, 26% of the patient population studied within the first 24 hours had complete coronary occlusion; 37% in the 24- to 72-hour group had complete coronary occlusion, and slightly over 40% had complete occlusion in the 3 to 7-day group (Fig. 3). The percentage of patients who had 70% to 90% obstruction did not differ significantly between the 3 groups. There was a trend in progression from subtotal to total occlusion. Almost every patient who had complete

coronary occlusion also had collaterals supplying the distal bed of the occluded vessel.

From these data, we conclude that complete coronary occlusion is infrequent during early non-Q-wave MI, and that coronary collaterals increase in parallel in patients demonstrating complete coronary occlusion.[3]

Coronary Thrombus in Non-Q-Wave Myocardial Infarction

Recently, we reviewed all coronary arteriograms.[4] We compared arteriographic findings with surgical

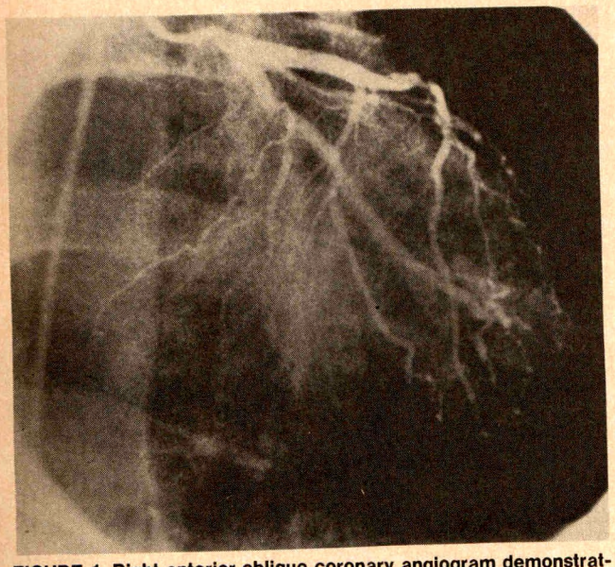

FIGURE 1. Right anterior oblique coronary angiogram demonstrating subtotal stenosis of the left anterior descending coronary artery. (Reprinted with permission from the New England Journal of Medicine 1986;315:417–423).

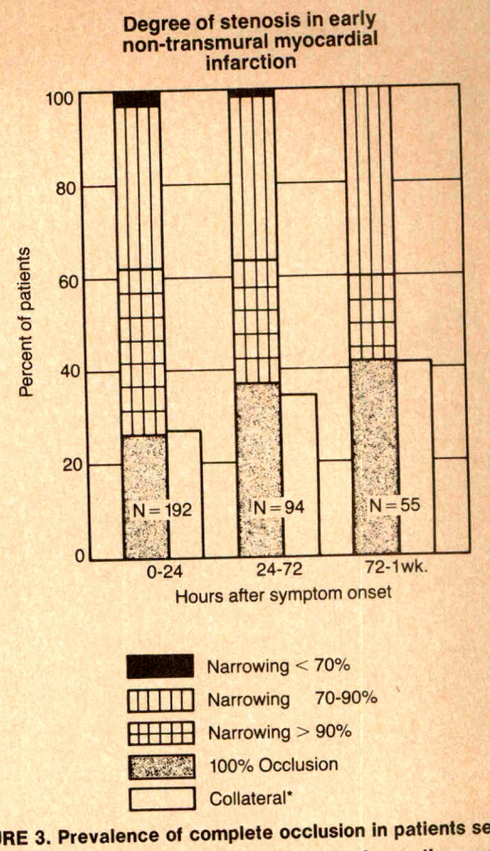

FIGURE 3. Prevalence of complete occlusion in patients seen during non-Q-wave myocardial infarction. As is shown, the percentage of patients with complete coronary occlusion increased over time and was dependent on the interval from symptom onset to the time arteriography was performed. Also demonstrated is the extent of coronary collaterals, which almost uniformly matched the increase in complete coronary occlusion. (Reprinted with permission from the New England Journal of Medicine 1986;315:417–423).

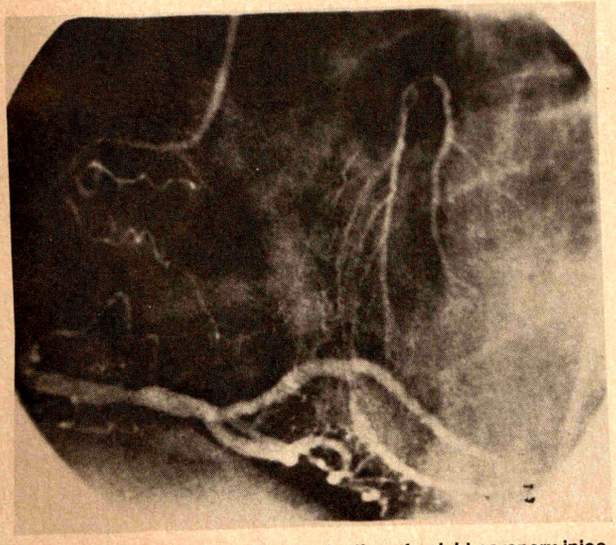

FIGURE 2. Left anterior oblique projection of a right coronary injection. The left anterior descending coronary artery is completely occluded. Collaterals are seen going from the right coronary artery to the distal left anterior descending coronary artery and the equal perforating branches.

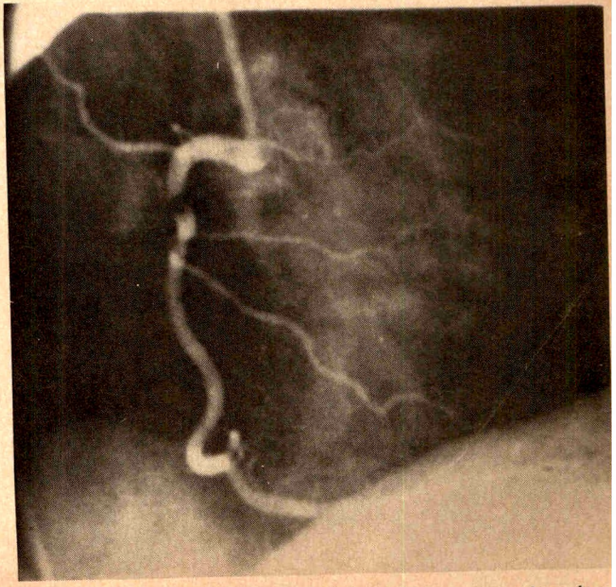

FIGURE 4. Coronary arteriogram of the right coronary artery demonstrating intraluminal filling defect. Thrombus was retrieved at surgery.

findings to determine how often coronary thrombus was present on arteriography. These data are currently undergoing further refinement. Most of the time, coronary thrombus was identified by a filling defect (Fig. 4). When patients did have complete coronary occlusion and obvious coronary thrombosis (identified by persistent staining of the infarct-related vessel), coronary collaterals usually filled the distal bed.

Conclusions

Although Q-wave MI is associated with a high frequency of complete coronary occlusion and infrequent coronary collaterals, we found that the reverse was true in early non-Q-wave MI. Likewise, preliminary data suggest that coronary thrombosis is much less evident on arteriograms in patients with non-Q-wave MI.

Because non-Q-wave MI is frequently associated with continued anterograde perfusion or perfusion via collateral vessels in the setting of complete coronary occlusion, the distal vessel can be visualized. Furthermore, because non-Q-wave MI is frequently associated with multivessel disease,[3] and preliminary data suggest there is a lower angiographic evidence of coronary thrombosis,[4] it is likely that strategies aimed at the treatment of multivessel disease in the absence of coronary thrombosis should be implemented. This is especially so since the mortality associated with non-Q-wave MI approaches that of Q-wave MI in the absence of interventions.

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Discussion V

Dr. Cohn (*Stony Brook, New York*): Dr. DeWood, when your study began, resolving questions about unrecognized non-Q-wave infarction probably was not a primary objective. Considering the emerging interest in silent infarction and ischemia, do you have any comments on the incidence of unrecognized non-Q-wave infarctions? It currently appears that unrecognized transmural infarctions account for about 25% of all myocardial infarctions.[1]

Dr. DeWood (*Spokane, Washington*): We believe the incidence of unrecognized non-Q-wave infarction is probably much less than Q-wave infarction, because the amount of myocardial involvement in non-Q-wave is much less. We reviewed more than 25,000 electrocardiograms with subendocardial ischemia earlier this year. These electrocardiograms were cross-referenced against those hospitalized patients with documented infarctions. The patients who had a diagnosis of transmural infarction (Q-wave infarcts) felt their infarct much more frequently than did those patients wiht non-Q-wave infarcts. The non-Q-wave infarcts were more likely to have indiscreet or intermittent symptoms, whereas the patients with Q-wave infarcts had a discreet onset of chest pain frequently.

Dr. Epstein (*Bethesda, Maryland*): Dr. DeWood, what do you think is the underlying mechanism responsible for the infarction?

Dr. DeWood: I'm not sure that I can answer that. It's convenient to have total coronary occlusion and a blood clot sitting in the coronary artery with staining. When these are retrieved, clearly platelet aggregates are seen mixed with fibrin. In contrast, the non-Q-wave infarction patients may still have small microaggregates and platelets going downstream that are causative of non-Q-wave infarction, but cannot be visualized by arteriography because they are beneath the resolution of the coronary arteriogram. There seems to be continued perfusion in the face of the MB-creatine kinase leakage from the myocardium. I think we need to focus on an interaction between microaggregates and other mechanisms of reduced flow, which is abnormal vasomotion.

Dr. Kupersmith (*Louisville, Kentucky*): Concerning the same study, if you were to use the TIMI [Thrombolysis in Myocardial Infarction Study] classification of arteriography, would the patients be toward grade 1 (minimal perfusion) or toward grade 3 (complete perfusion)? Secondly, were there many exercise-induced infarcts?

Dr. DeWood: There were no exercise-induced infarcts. With regard to the TIMI classification, most would be between 2 and 3. We saw the distal vessel quite a bit of the time through the primary vessels, not necessarily with collaterals.

Dr. Kennedy (*St. Louis, Missouri*): In the course of this meeting, we have all agreed with the idea of educating the public about the phenomenon of silent myocardial ischemia, and have tried to understand early prognostic data. Dr. Krucoff's paper is very important, because we need to also focus on the technical and quality control in aspects of diagnosis. As members of the Council on Silent Myocardial Ischemia & Infarction, we need to start thinking about the practicality of teaching this information. In clinical practice, our patients get a 12-lead electrocardiogram, with the lead placed where there is maximal ST depression. But the minute we start going back on old data bases, we resort to a V_5 lead. There is no question about how much ischemia might be missed through lack of a V_3 or an aVF. Where are people going to go out and put these leads? I had hoped that our earlier discussions would focus more on the emerging technical and quality control problems that surround the diagnosis of silent myocardial ischemia. Even with a controlled environment and controlled angioplasty inflation, we can see changes in sensitivity by having an additional lead. Three-channel electrocardiography is in the marketplace now. However, the state of commercial manufacturing is such that, although ST depression goes down in 1 channel, the J point doesn't. The ST segment goes out 80 ms from the J point, and when it gets depressed, we see it. What we need to do is to examine ST changes in real time, print them out, and make sure they are valid. Technically, we are at the brink of this capability. The commercial manufacturers are working on algorithms that detect J-point depression. So, although 3-channel systems are available, remember that a controlled environment, as was present during Dr. Krucoff's study, won't exist in your hospital. There will be patients with minor ST-segment changes, and if you consider these recordings a valid representation of significant ST depression associated with ischemia, you will be fooled a great deal. So, I just wanted to provide a little focus, because I'm being asked in Dubuque, Iowa, "Dr. Kennedy, what leads do you use?" And I say, "There are some data on aVF and V_5, and we are exploring that." These types of practical questions are going to start emerging this year.

Dr. Cohn: While not disputing the benefits of multiple leads, exercise testing and Holter monitoring have both shown that V_5 yields a lot of information. However, it may not be the complete story and, in fact, can underestimate the amount of silent ischemia present. The addition of newer technology, rather than casting doubt on anything that we have learned thus far, can only further show what a widespread phenomenon silent ischemia is, and how much it affects the daily lives of our patients.

Dr. Epstein: There is a potential limitation of that. Whenever sensitivity is increased, specificity decreases. I'm not questioning what happens in the cath lab, but in everyday practice, a single lead, while it picks up fewer episodes of ischemia, may detect those that are more dangerous from a prognostic view. And, if you miss it with V_5, it may not be important. So, one has to consider that part of the sensitivity/specificity issue as well.

Dr. Hollenberg (*San Francisco, California*): Just to amplify upon Dr. Kennedy's remarks, analysis of Holter recordings is still a very labor-intensive technology. Some additional cautions: If you monitor at a fixed spot, that is, at J plus 80 ms or J plus 60, and ignore what happens at the J plus 0 point, then with just transient T-wave changes, as may occur with positional changes, you'll be classifying changes as ST-segment depression that, in fact, are not ST-segment depression, but are only T-wave changes. We never monitor the ST at longer than J plus 60 ms. Once heart rates start approaching 115 to 120, even J plus 60 falls within the rising or falling slope of the T wave. So if we are moving toward more automated analysis, there has to be a variable J-point sampling spot, which is heart-rate sensitive, and you cannot sample at only 1 point in a 24- or 48-hour period. Not only is there a need for better automated algorithms that can sense heart rate and RR intervals, but we need to have algorithms that accurately sense the J points. Currently, proper analysis of Holter tapes is a very labor-intensive period of time, where the technician has to sit in front of that monitor and keep adjusting the sampling point, not only at the J plus 60 or 40, but at the J, because QRS complexes continuously vary in width. It is misleading to think that these systems are really totally automated.

Dr. Amsterdam (*Davis, California*): Concerning technical aspects of monitoring, something has plagued me about interpretations of the exercise electrocardiogram: how to analyze the electrocardiogram if the ST segment is abnormal to begin with. That becomes very difficult to understand, because the abnormal, chronically depressed ST segment is a more labile ST segment and can lead to a lot of false-positive responses in the absence of coronary disease. What do we do in Holter monitors? A lot of people with coronary disease, for example post-MI patients, have diffuse ST abnormalities. How do we interpret that? In the exercise lab, we arbitrarily call for an additional 2 mm beyond an already depressed ST segment. That gives the best trade-off between sensitivity and specificity. It may or may not be the right thing to do. Dr. Cohn, what do you do with the Holter?

Dr. Cohn: We've had a lot of experience with exercise testing. However, with the Holter, I think it is prudent to avoid leads in which there are anything more than very minor ST-segment abnormalities.

Dr. Kennedy: Perhaps this is an appropriate time to establish a criterion of 2 mm below persistent ST-segment *depression* and examine that for predictive value. Dr. Amsterdam's point is absolutely correct. The very people who need this are those who have recurrent coronary artery disease. They may have had a bypass or angioplasty, they often have a scar, and we've got to deal with them.

Dr. Cohn: I am not disputing that. But as of right now, if someone comes to you with lead V_5 showing 3-mm ST depression and criteria for left ventricular hypertrophy, you know as well as I do that you are not going to be able to interpret any further ST depression in a meaningful way.

Dr. Pepine (*Gainesville, Florida*): Listening to us talk, one would think the sensitivity/specificity issue is a trade-off and is going to get worse the more we start sampling. But in fact, it hasn't worked that way. The Multiple Risk Factor Intervention Trial is probably the best example of that.[2] A computer-read electrocardiogram was used to examine the area between the baseline and the ST segment. When physicians read the electrocardiograms, as we do now—with the Holter recording in a true positive/negative fashion using the criterion of 1-mm depression—they identified very few ischemic responses. Only when using the computer-processed electrocardiogram to assess the area of ST-segment depression did the high-risk group emerge. It seems the more technology we use to refine our assessment of the ST segment and perhaps the entire electrocardiographic signal, the more specific for ischemia, and hence high risk, we will become.

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Diagnostic and Therapeutic Considerations in Silent Myocardial Ischemia

JOHN S. SCHROEDER, MD

Attempts at diagnosis and treatment of silent myocardial ischemia appear to be justified in patients with known or suspected coronary artery disease. A positive exercise test result or ambulatory electrocardiographic monitoring showing ST-segment deviation is an appropriate indication for adjustment of anti-ischemic therapy. With the documentation of more severe ischemia, angiography should be considered to determine the extent of coronary artery disease. Medical therapy, antianginal agents and risk reduction may improve survival. When ischemic involvement is severe, as in 3-vessel disease, interventional surgery may be required, whether or not ischemia is accompanied by angina. Selected clinical practice cases are presented to illustrate these diagnostic and therapeutic considerations, and are followed by group discussion.

(Am J Cardiol 1988;61:41F–47F)

The physician concerned about silent myocardial ischemia faces a number of unresolved questions. Among the most clinically pressing are: What is the best way to detect silent myocardial ischemia? How often should screening tests be performed for silent myocardial ischemia? How should patients with silent myocardial ischemia be managed, once diagnosed?

Approach to the Patient with Silent Myocardial Ischemia: Current Considerations

Despite advances in current knowledge about silent myocardial ischemia, many questions remain unanswered in the quest to formulate a clinically rational approach to this problem within the realm of existing diagnostic and therapeutic capabilities.

For instance, how sensitive and specific is a positive treadmill test for identifying patients with silent myocardial ischemia? Is it really necessary to look any further for silent myocardial ischemia if a patient has a negative treadmill test result, i.e., one that shows no ST-segment changes?

If the treadmill test response is positive, can the number of episodes of ST depression be used as a therapeutic marker rather than reliance on a report of symptoms? It is well known that objective evidence of ST depression or ischemia has important prognostic implications. However, should physicians be as aggressive in treating the asymptomatic patient as they are in treating the symptomatic patient who has ST depression on the exercise stress test? If so, what criteria provide a reliable indication of therapeutic efficacy? Is the patient going to be treated until there is <1 or 2 mm of ST depression, or is it enough to require less ST depression at maximal exercise?

How do Holter monitoring studies fit into the diagnostic scheme, and are they really necessary to follow the progress of treatment? It would be simpler to just repeat the treadmill test in the patient who is able to exercise. Should therapy for patients with silent myocardial ischemia be adjusted according to review of follow-up ambulatory electrocardiographic studies? Perhaps Holters are only necessary in patients unable to exercise.

Group Discussion

Dr. Schroeder: Dr. Parmley, how do you use the exercise treadmill test to make management decisions in patients with suspected silent myocardial ischemia?

Dr. Parmley: If the treadmill identifies ischemic-type ST-segment depression in the asymptomatic patient, my next step is to have the patient wear a Holter monitor to see what happens in the work and home environment. If it shows no ischemia, I feel a little bit more comfortable. If the Holter shows ischemia, I try to associate it with a precipitating stimulus.

Dr. Schroeder: So if you have a positive treadmill test, you almost always do a Holter, even in the asymp-

From the Coronary Care Unit, Stanford University Medical Center, Stanford University School of Medicine, Stanford, California.

Address for reprints: John S. Schroeder, MD, Cardiology Division, Stanford School of Medicine, 300 Pasteur Drive, Stanford, California 94305.

tomatic patient. But with a negative treadmill, you might not.

Dr. Pepine: Clinical experience has shown that if a patient has a high-level negative treadmill, he is unlikely to have ischemia identified on an ambulatory monitor. A few additional cases can be detected by adding an ambulatory monitor—probably those related to spasm.

Dr. Schroeder: But is that really worth the expense of doing Holters on many patients?

Dr. Parmley: One of the more important things to keep in mind is what we are trying to do. The goals of management are to prolong life, i.e., reduce mortality, and to reduce the incidence of such cardiac events as myocardial infarction. Very few interventions in coronary artery disease have been shown clearly to do that. So, getting to your first question, an asymptomatic patient with a high-exercise negative treadmill has less than a 1% chance per year of dying, and less than a 3% chance of developing some coronary event. Frankly, the likelihood of intervening beneficially in that patient is so low, based on current data, that I would not do anything else. The negative treadmill alone puts the patient in such a good risk category that, unless there was some other factor that would affect this patient's outcome, I would go no further.

Dr. Schroeder: What about a 48-year-old patient with a positive treadmill showing 1.5 mm of ST depression without pain at a heart rate of 116 beats/min. Would you do a Holter?

Dr. Parmley: We are dealing with about a 75% sensitivity and specificity. Depending on the population, statistically there are more false-positives in patients who have a low risk of having the disease. If silent myocardial ischemia was suspected, an independent test for ischemia, such as a thallium scan, would be appropriate. Some could argue that a radionuclide ventriculogram with exercise or other test might be as effective but, currently, the next step would be to obtain an independent marker of ischemia.

Dr. Schroeder: Is there any group, for instance those with known angina, in whom you would use the treadmill test to adjust medications?

Dr. Pepine: No, because adjusting medications to change the treadmill response has not been proven to alter prognosis.

Dr. Schroeder: Then why bother performing repeat treadmill tests to look for silent ischemia?

Dr. Pepine: Once you identify a high-risk treadmill, i.e., 2 mm of ST depression, prolonged recovery, ST shifts at a low work load—nothing can erase it. In my view, even if 5 more treadmills were negative, they would not override the importance of 1 positive test.

Dr. Parmley: The issue is whether there is data to prove that treating ST depression has a beneficial effect on either myocardial infarction or mortality. Currently, there is none. We know that ST depression, like arrhythmia and depressed left ventricular function, is an independent marker of poor prognosis and should be measured in the high-risk patient by some technique. Therefore, it would certainly seem that if ischemia could be reduced in the same way that we reduce arrhythmias, these patients would live longer. In patients with chronic heart failure, the association between improved ejection fraction and prolonged life is well known. But in the hope of benefiting the patient, I think we could consider treating silent ischemia either medically or, more aggressively, by interventional therapy...including surgery. Again, we are left with the dilemma of recognizing factors that identify high-risk patients, and ischemia is certainly one of them, but we are not sure that treating it has a beneficial effect.

Case 1: The Patient with a Positive Thallium Scan

A 73-year-old man who had a positive result on thallium study in 1984 had not been given any antianginal medicine. He had been followed at Stanford Hospital for about 11 years for mixed lymphoma, had an excellent response to therapy, a normal electrocardiographic result and was asymptomatic. During a treadmill test, the patient exercised for 4.7 minutes with no angina, but experienced a decrease in blood pressure.

Group Discussion

Dr. Schroeder: Dr. Pepine, what would be your approach to this patient?

Dr. Pepine: I would consider this a high-risk treadmill response, with at least 2 markers for ischemia. The patient is also high risk because of such independent variables as age, sex, etc. Therefore, I would proceed immediately to coronary angiography.

Dr. Cohn: What about the ST response during exercise?

Dr. Schroeder: The patient really had minimal ST displacement; the primary abnormality was a drop in blood pressure.

Dr. Cohn: Why did he stop exercising?

Dr. Schroeder: Fatigue.

Dr. Amsterdam: Could you tell us a little bit more about that blood pressure response? Was there an initial elevation? Were there any symptoms when blood pressure dropped, and was this a true exercise-induced blood pressure drop?

Dr. Schroeder: The patient really only got into stage 2 of the Bruce protocol, so there was only 1 additional blood pressure and it was slightly elevated before falling.

Dr. Amsterdam: The patient has not had a previous infarct or aortic stenosis?

Dr. Schroeder: No, but he did have a positive thallium.

Dr. Amsterdam: Right, but that is not what usually gives you a blood pressure drop.

Dr. Parmley: How positive was the thallium scan?

Dr. Schroeder: We don't know, since it is only referred to in his history as being "positive" 3 years earlier.

Dr. Parmley: But the details of that must be very important. What we all know from experience is that

there can be an apical defect in thallium scans. In this age group, that might be a relatively nonspecific high incidence of false positives.

Dr. Epstein: I think we ought to ask: On the basis of the data we know in this 73-year-old man, what is the chance of him having a MI or dying of ischemic heart disease over the next 5 years?

Dr. Amsterdam: Taking it 1 step further, what is the chance for preventing such a coronary event, say with coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty? Based on the information you presented, I don't think I would do coronary angiography in a 73-year-old man with a mixed lymphoma who is asymptomatic.

Dr. Schroeder: So, despite exercise-induced hypotension and a short exercise time, you feel his expected survival is not sufficiently jeopardized to intervene?

Dr. Epstein: Well, I think your information is not specific. Besides the thallium study in 1984, of which we have no details, there is no objective evidence of ischemia; the patient doesn't have pain or ST-segment depression. I certainly would not go ahead with coronary angiography because of what Dr. Parmley has pointed out.

Dr. Schroeder: But aren't there many people who feel the post-MI treadmill showing poor exercise time is actually a better predictor than ischemia?

Dr. Amsterdam: That is a different setting; you know the person has myocardial damage. This could be a deconditioned older man who can't do very well. He has a VO_2 that is over 15, he is 73, he may not be that different from other sedentary 73-year-old men. There is nothing specific on that treadmill, and based on the information shown, I am not convinced about the blood pressure response. If the blood pressure really rose and then fell and the blood pressure was dropping, that would be convincing. What's up there is suggestive, but it's not convincing.

Dr. Schroeder: The patient's exercise electrocardiogram showed significant ST depression during stage 2 of the treadmill test, so we proceeded to coronary angiography. The patient had about a 60% left main lesion, and some disease elsewhere. He went on to uneventful coronary bypass surgery in the hope of prolonging life.

Case 2: The Patient Hospitalized to Rule Out Myocardial Infarction

A 59-year-old man was hospitalized to rule out MI. He had a small increase in myocardial enzyme levels, suggesting subendocardial MI or unstable angina. The patient's condition stabilized in the hospital and he performed a treadmill test about 3 or 4 weeks later, which showed inferior ischemia. Coronary angiography showed very diffuse disease in the left anterior descending artery, an occluded circumflex artery, an occluded mid-right, and mild anterior hypokinesia. The patient was considered to have nonoperative coronary disease. Because of his inoperable state and the diagnosis that ruled out MI, the risk for subsequent cardiovascular event was considered to be extremely high. The patient was prescribed maximal doses of diltiazem, 90 mg 3 or 4 times daily, along with small doses of β blockers. Annual follow-up treadmill testing continued to show silent ischemia. The patient, who has been followed for 5 years, averages 1 episode of angina a month, but otherwise is asymptomatic.

Group Discussion

Dr. Schroeder: This man has a normal electrocardiogram and an excellent ventricle at rest, but has absolutely terrible coronary disease. His treadmill shows marked ischemia, not only inferiorly, but in some of the other leads. Repeat treadmill showed a normal resting electrocardiogram, but even more dramatic ST depression with no pain at a heart rate of about 90 or 100 beats/min. Should this patient have Holter monitoring, or should he have a thallium scan to evaluate risk and help determine which vessel should be bypassed? Or, should the same regimen, which has worked well for 5 years, be continued?

Dr. Pepine: Rejection for surgery in 1982 doesn't mean that the patient would necessarily be turned away again in 1987.

Dr. Schroeder: Should the coronary ateriogram be repeated?

Dr. Pepine: Remember, the quality of these films in 1982 was not as good as it is now, nor were surgical capabilities the same. Contemporary surgeons are more ambitious with endarterectomies and other procedures. Several times, people have been referred to me with that kind of a film in their records, and they turn out to be surgical candidates after all. That would be one thing that I would do; otherwise, there isn't much more that could be done diagnostically. The patient has been documented to have a lot of ischemia, and has been maximally treated with anti-ischemic medications. So, the major question here is whether or not to perform surgery.

Dr. Cohn: Suppose the patient controlled his activities to prevent ischemia out of hospital? Would you feel better about him then?

Dr. Schroeder: Not necessarily. The patient is a very active fellow who plays golf. He gets angry easily. He has a couple of children in their late teens. I think that even if the Holter didn't show much, there are certainly going to be times in his life that he's going to have ischemia whenever he gets a heart rate of 90 or 100.

Dr. Cohn: So, actually, that would make you feel worse than if you did the Holter and found out that he had many episodes.

Dr. Parmley: This patient throws clubs on the golf course, he's a high-stress, major-risk individual. Dr. Pepine's point to reconsider any possibility of revascularization was an important one. I, too, would treat with anti-ischemic agents at doses that provide protection from angina but can be well tolerated. I'm not sure Holter monitoring would be beneficial. The patient is already at maximal medical therapy, and you know he has ischemia when he exercises. I think I would tend to stay with that regimen.

Dr. Epstein: I don't think CABG is applicable to this patient. We don't know what his left ventricular ejection fraction is, but he has a normal rest electrocardiogram. So there is a good chance that he has normal left ventricular function.

Dr. Amsterdam: If the man limited activity to avoid exercise-induced ischemia, would that make you feel better and would it change his prognosis? It's a very interesting issue. We like to keep people away from the threshold level of ischemia because intuitively, it sounds prudent. But we don't have good data that it will change the outlook. The important thing is, the treadmill identifies a risk factor for poor prognosis, not a risk factor if the person exercises at that level. We don't know that it's at that work load or at that heart rate that he will get in trouble. So, to be prudent, we might keep the patient below that level of activity. But, the treadmill is just 1 risk factor.

Dr. Schroeder: And we know that most people don't have a myocardial infarction during exercise or even golf. He's retired and golf is important to him and I've not restricted that.

Dr. Cohn: To me, simply reviewing the films again is not the answer. There is a good chance that the patient is still not going to be considered operable. What can we do for him then? We need to empirically maximize medical therapy. The patient has to be put on medication titrated to the point of side effects, or we are not doing our job. We cannot assume surgery is going to answer our problems.

Dr. Schroeder: And there, I think the Holter might be more helpful.

Dr. Pepine: This patient has a real need for Holter monitoring, because we certainly don't want to make him worse. Blindly adding another calcium blocker to the diltiazem regimen can potentially increase ischemia. So, in this totally asymptomatic man, I would use the Holter to guide therapy.

Dr. Kupersmith: There is absolutely no validation for using either Holter monitoring or the stress test for assessing therapeutic endpoint. In a man with this much coronary disease, there is no way to prevent ischemia, even if you happen to see some reversibility on a 24- or 48-hour Holter. The goal would be to achieve maximum tolerable medical therapy.

Case 3: The Patient with a Strong Family History of Coronary Artery Disease

A 48-year-old bread salesman, who appeared in excellent condition and had no known coronary disease, was referred for evaluation because his brother had coronary disease on a routine treadmill test. The patient had a strong family history of coronary artery disease, smoked, and had markedly abnormal lipids, so was an excellent candidate for treadmill evaluation. Resting heart rate was 60 beats/min, which increased to 135 with a mild fall in blood pressure. The patient rapidly recuperated and exercised about 6 minutes without pain, but had about 3 mm of ST depression in the inferolateral lead.

Group Discussion

Dr. Schroeder: Should this patient have coronary arteriography, or should he have a Holter or thallium scan first? What should be done for this patient to ensure the best chance for a normal life?

Dr. Becker: I don't think a thallium scan is necessary when the exercise test is as strongly positive as this one.

Dr. Schroeder: Results of coronary angiography showed 3-vessel disease and multiple lesions in the right coronary artery. The patient has multiple proximal and mid-left anterior descending lesions, as well as some distal left anterior descending and obtuse marginal disease. Based on these findings, we considered the patient a candidate for CABG, even though he had absolutely no symptoms and a normal left ventricle. I was quite convinced in 1980 that CABG was going to save the patient's life. So I had to face this person who had never had any symptoms and recommend CABG, which would disable him from his job for several months. He looked me in the eye and said, "You mean despite the fact that I don't have any pain, this is serious?" Maybe today he would have been considered for angioplasty. The patient had a routine CABG, which went well. He was discharged on Anturane® therapy, which was the medicine of the year. Because the patient never had symptoms, the only way I could really follow him was with a yearly treadmill. The first treadmill looked good. The patient had taken my advice about exercising seriously. Consequently, he achieved a high heart rate, with a markedly improved exercise capacity. He continued to be asymptomatic. For the following year, he still had a normal electrocardiogram, with excellent exercise tolerance (he was able to exercise for 13 minutes). The third year, however, the patient began to show the first signs of ischemia in the lateral leads. Since ischemia had appeared at a high heart rate, the patient was not given anti-ischemic medication. Over the next year or so, the patient continued to have excellent exercise tolerance without the development of hypotension, but the ST depression was becoming more dramatic and more severe. His last treadmill showed marked ST depression in leads II and V_5 during exercise stages 4 and 5.

Dr. Schroeder: Does this patient need another coronary arteriogram and possible repeat surgery? He has never had a symptom. Do you think he is going to believe me if I tell him that? Should I have put him on medication?

Dr. Pepine: I don't agree that these treadmill responses are as serious a prognostic problem as you identified previously. The patient's blood pressure doesn't drop. He goes to stage 5, whereas he only exercised for 4.3 minutes the first time. So, from a prognostic standpoint and in terms of markers, the patient looks better. Secondly, from what we know about the conduits that were used in 1980, I wouldn't be surprised if at least 1, and possibly 2, are functional or occluded. Whether or not disease has progressed

not is debatable, but most likely it has. I wouldn't do anything immediately. I would, however, start mentioning to the patient that he is approaching the limits of therapy for a generally progressive disease, and I'd start preparing him over the next year or 2 for additional intervention. When the stress test again shows him at a high risk, then I would proceed with coronary angiography.

Dr. Schroeder: How about a thallium study to detect the degree or extent of myocardium at risk?

Dr. Pepine: I probably wouldn't do that right now. I would be happy with the treadmill.

Dr. Parmley: Let me just ask a couple of questions. I assume that you vigorously intervened to reduce risk factors?

Dr. Schroeder: I did. The patient does not smoke anymore, and is taking fish oils, with some response in triglycerides, but they remain quite high—around 200 to 300 mg/dl. His cholesterol averages 300 mg/dl.

Dr. Parmley: Is he currently being treated with anti-ischemic medication?

Dr. Schroeder: No. That's really one of the questions here.

Dr. Parmley: I concur with Dr. Pepine in terms of prognosis. Looking at your data, the patient is at a different point now. It would be reasonable to consider some anti-ischemic medication, if he can tolerate it. I would not do a thallium scan, because I'm not sure how it would further help at this point. Since there is good exercise tolerance, with a reasonably high heart rate and no drop in blood pressure, the patient tends to fall out of the high-risk group. So I would not do a thallium, but I might consider some anti-ischemic therapy.

Dr. Schroeder: Should I test the patient again after a course of diltiazem, or is it safe to assume it's going to protect him?

Dr. Parmley: I don't see any reason to titrate the diltiazem, if that's what you are asking.

Dr. Epstein: Just a point about the post-CABG patient. There are no data on the prognostic value of ST segment deviations in the post-CABG patient; it may or may not be analogous to that in the virginal patient. There are so many differences that I don't think we can use the treadmill with the same degree of prognostic certainty as we do with a patient who has not had a CABG. A second bypass carries with it an appreciably higher risk than a first bypass procedure. If you decided to do percutaneous transluminal coronary angioplasty, the risk would also be higher. So, I think that the risk/benefit ratio is going to be altered by the greater risk of interventional therapy. I would not, at this point, perform repeat coronary angiography, because would not reveal anything that would lead me to recommend percutaneous transluminal angioplasty or bypass surgery in this post-CABG patient.

Dr. Krucoff: Dr. Epstein, would you agree that the lower heart rate response and the lack of hypotension on the treadmill is a much better prognostic sign that ST-segment changes?

Dr. Epstein: Yes, I would agree with that. I'm wondering, however, about the choice of diltiazem as opposed to a β blocker.

Dr. Schroeder: Because the patient is basically healthy, and if he became impotent because of β blockade, I would also have created another disease. Diltiazem is very well tolerated.

Dr. Kennedy: I absolutely agree with the perspectives of Drs. Pepine and Parmley, but I want to come back to this because as with the arrhythmia issue, we are discovering a phenomenon and instituting therapy with no idea of what the therapy is doing. To institute a calcium channel blocker in the belief that it will decrease ischemia is absolutely correct. But, just as we discovered about proarrhythmic effect, we have no idea now of what the treadmill is going to be. If we start anti-ischemic therapy, let's look at the results of it. I agree that we must try to modify mortality and morbidity. We hope to do that and to stop infarction. All of us know that this is a progressive disease. We are all thinking that we have to do coronary angiography at the appropriate time and try to prevent infarction. But we don't know if therapy creates a proischemic effect. So, we have to examine whether or not therapy had any benefit.

Dr. Parmley: I think the proarrhythmic effect of the antiarrhythmic drugs is pretty standard at 10%, or maybe more. A proangina effect of antianginal agents—for instance, reflex tachycardia—is occasionally seen with drugs like nifedipine, but it's extraordinarily uncommon. So I don't think a repeat treadmill is necessary to rule out a proangina or proischemia effect, but I do agree with the notion of trying to assess therapeutic efficacy. A repeat treadmill showing that the ST depression was 0.5 mm more or less would not necessarily influence clinical management.

Dr. Kennedy: Let's quantitate this. If the initial dosage of diltiazem has no anti-ischemic effect, I would increase the dose to 90 mg every 8 hours, and then higher. If there was less ST-segment depression in fewer leads, I would try to determine what constitutes anti-ischemic effectiveness. There is tremendous analogy to what we know about arrhythmias: the same variability factors, and the same applications. This is all new knowledge and we can't skip over it.

Dr. Pepine: I agree with your concept. There is no question that we ought to be looking at the potential for risk, but I don't like the idea of equating ischemia with arrhythmias. First of all, we have good drugs for ischemia, which are very unlikely to increase ischemia. Our drugs for arrhythmias are very poor and can cause a 10% or more incidence of proarrhythmia in patients who need therapy the most. No one feels that a little ischemia is good, but all of us have inconsequential premature ventricular contractions while we are sitting here. So the 2 are not alike. This patient reminds me not so much of a coronary bypass case, but of what we see every day with angioplasty. This patient with multivessel disease had angioplasty last year, and that's what his treadmill looks like now. So, Dr. Epstein, without all of the compounding influences and

the reduction in the risk/benefit ratio provided by previous bypass surgery, would you feel differently about how far you would go with this patient, compressing time to months instead of years, and given this exercise test?

Dr. Epstein: I would completely agree with the implications. I would treat this patient totally differently from the way I would treat a post-CABG patient. Given the recurrence of profound ST-segment depression, I would repeat the angiogram and I would consider repeating percutaneous transluminal coronary angioplasty.

Dr. Amsterdam: I think the treadmill is reliable in this post-CABG patient because, after surgery, he apparently returned to a normal baseline on the treadmill. So the compound variables may not be there. If a negative treadmill later becomes positive, it is highly unlikely to be a false positive. So, a negative treadmill followed by a positive one means ischemia has been reestablished. The patient's heart rate was tremendous-it looked like it was in the 160s or higher. At what heart rate did it become positive? To me, the heart rate at which the patient initially became ischemic is more important than the number of millimeters of ST depression at maximum.

Dr. Schroeder: It looks like 1 mm of ST depression at a heart rate of 111 beats/min and about 2 mm at 128 beats/min.

Dr. Amsterdam: That's low heart rate, so I would take a different viewpoint. I definitely would do a thallium scan to determine the extent of myocardial involvement and provide a much greater perspective than the treadmill. This doesn't mean I'll necessarily do an angiogram. Once the thallium is done, I can make my next move. If the person is positive at a low rate and has a drop in blood pressure, this is a bad response. A drop in blood pressure is a very unusual finding. Most high-risk patients are high risk based on ischemia at a low heart rate, without a drop in blood pressure. It's an extremely unusual finding and is not necessarily a key tip-off. Its predictive accuracy is very good, but its sensitivity is minuscule.

Dr. Krucoff: I, too, would take this gentleman back to the catheterization lab for several reasons. First, since the ST changes are in similar leads, we know he is post-CABG, and his anatomy is clearly not the same as was visualized initially. Second, in a post-CABG patient, which is an increasingly common subgroup, there is at least the potential to intervene with angioplasty revascularization in a partially protected scenario. There may be a compromised rather than an occluded graft, and you may be able to work on a native vessel with some distal circulation, despite what's being done through that graft. Given that there has been such a clear change in this patient's ischemic activity, waiting until he again becomes high-risk may force a second operation or render the patient intractable to medical therapy. Now may be exactly when you could intervene in a semiprotected environment and help him with angioplasty.

Dr. Cohn: Suppose this man presented again with the same exact story, good ejection fraction and so forth, same exercise response, same catheterization data, except that it is 1987, and the medical vs surgical longevity for 3-vessel disease with left ventricular function is pretty similar. What would your inclination be now?

Dr. Schroeder: I think it would be the same, just because it is my bias that these patients, even though there may not be a difference in mortality, are still at high risk for infarction or other type of cardiac event that may not result in death, but can cause disability.

Dr. Epstein: I admit that we don't have very good longevity data, aside from Erikssen's study in totally asymptomatic people, so are forced to make clinical decisions with incomplete information. If a person has significant ST-segment depression—and I would do a gated blood pool study to confirm that there is inducible ischemia—in the presence of 3-vessel disease, I would consider that patient to be at high risk of death and would recommend revascularization . . . even in the absence of symptoms.

Dr. Cohn: If the patient fell into a high-risk group, with profound ST-segment depression and profound ejection fraction on exercise, you would consider this man bypassable in 1987?

Dr. Epstein: Absolutely, but I disagree slightly with Dr. Krucoff. If angioplasty is done, 3% to 5% of these patients—even those with 1- or 2-vessel disease—run into trouble that necessitates an urgent bypass operation.

Dr. Krucoff: Except that he may be in a more protected group. If he has a graft to distal circulation, you work on a native vessel.

Dr. Epstein: I'm just saying that it's a different risk situation. Perhaps I'm intrinsically a little more conservative but have a higher threshold in doing invasive therapeutics in a patient who has already had bypass surgery, because of the higher risk if problems develop.

Dr. Hollenberg: What about the recovery phase?

Dr. Horwitz: I agree that looking for a drop in blood pressure frequently is unrewarding. I think that you shouldn't lose sight of the point that Dr. Pepine made. This man has superb exercise capacity. At whatever level he's beginning to develop ischemia, the most disturbing thing is that there is a change. We should get the maximum amount of information about that change. It would also seem that this patient is an ideal candidate for a Holter monitor. For example, ambulatory electrocardiography showing multiple persistent episodes of silent ischemia signifies the need for aggressive intervention. If there was nothing—no arrhythmia and no ischemia—I think you'd feel a little better about it. I don't think that this man on a gated is going to suddenly deteriorate at a moderate load...n with the kind of exercise performance he is showin on this test. He's not a high-risk exercise test. But think what we are all trying to do is to pick the point which we may intervene. The patient is beginning show signs that his initial therapy hasn't been ve good. He is still probably not at an enormous risk. B the maximum information you can get would be hel ful so, since symptoms can't help you, perhaps a Holte could.

Dr. Hollenberg: I can't let this discussion go without commenting on exercise testing. We need a quantifiable, reproducible test. We have ignored many variables in this exercise test, that is, his ST changes occur late so he has late evolutionary changes, and they resolve fairly quickly. These are all hallmarks of mild involvement. We also know that his exercise duration is quite excellent. Sure, the patient gets ST depression at 13 minutes of exercise, but by 2 minutes of recovery, he is almost back to normal. So I think you have to quantify the changes that occur in evolution and resolution, and, in fact, we have a treadmill exercise score that quantifies all of these variables. I have found that a very reproducible, quantifiable exercise test can identify either significant graft occlusion or new lesions in the native vasculature in many patients. So, a quantifiable reproducible exercise test is a very helpful technique to follow post-CABG patients. It also is a very subjective test; the patient stops at variable endpoints according to how he feels that day, and it is very hard to quantify him, unless one uses all these complex features. To still look at this the way we read exercise tests 20 years ago is really a little simplistic, and I think we are shortchanging the information that we do gain with the exercise test.

Case 4: The Postmyocardial Infarction Patient

A 69-year-old man had an inferior MI and was treated with intravenous streptokinase. Recovery was uneventful. Because stenosis was not severe, angioplasty or CABG was considered unnecessary. The patient, who had very few risk factors, remained asymptomatic during treatment with diltiazem and aspirin. Several months after MI, repeat treadmill testing showed evidence of lateral wall ischemia, despite good functional capacity and no chest pain. The resting electrocardiogram showed a small inferior MI, and there were small Q waves between leads III and aVF. But during exercise, it appeared that this inferolateral area was still in jeopardy. Recovery at 3 minutes showed significant ST depression. Because the patient was asymptomatic, the dosage of calcium blocker was reduced despite the marked ST depression. The patient returned 6 months later feeling better than ever, still asymptomatic. A repeat treadmill looked about the same, and functional capacity was normal. There was residual evidence of an old inferior MI, with ST depression at stage 3. Exercise was stopped at stage 6 of the Bruce protocol and a heart rate of 150 beats/min. Marked ST depression subsided rapidly.

Group Discussion

Dr. Schroeder: Again, the question is what to do for this patient.

Dr. Pepine: What was angiographic anatomy after the infarct?

Dr. Schroeder: The patient had about a 50% mid-right lesion and a normal left system. So, he was felt not to require angioplasty.

Dr. Pepine: This is becoming more common in our postrevascularization patients, where we see much less than 50% narrowing in the revascularized vessel or in the reperfused vessel, with a very abnormal exercise response. I attribute some of this to the abnormal resting electrocardiogram, with those T-wave inversions. However, I don't think this is the whole picture. I can't attribute it all to a gross underestimate of the significance of the stenosis from the coronary arteriogram. I don't know what it means prognostically. I probably would have treated this patient with a Q-wave infarction with a β blocker, and I don't know that I would have done anything differently, Dr. Schroeder, than you have.

Dr. Parmley: This is more than a year postinfarction at this point?

Dr. Schroeder: It is now about a year postinfarction.

Dr. Parmley: So, the patient has gone through the "high-risk period," i.e., he hasn't died in the first 6 weeks, 3 months or 6 months. He has documented coronary artery disease, which was only right coronary artery disease 1 year ago. This is really a difficult case to become overly aggressive with at the moment, with superb exercise tolerance despite the ischemia shown there. In the absence of any other data, I am not sure that I would recatheterize the man at this point. I would probably err on the side of conservatism.

Dr. Schroeder: Should I increase his diltiazem, or decrease it? The dosage was decreased because the patient had no pain on the treadmill. However, I am not sure it made much difference. He is on 60 mg 3 times a day.

Dr. Parmley: That is a reasonable dose, although not a maximum dose, so I am not sure I would be persuaded necessarily to push at this point.

Dr. Krucoff: I would pursue this patient at least with a thallium scan or similar to look at the actual anatomic perfusion defect. If there is none, I think I would use his symptom-free, high functional capacity status to keep withdrawing diltiazem. If, on the other hand, there was a clear-cut defect, I would more strongly consider angiography. Clearly, in 3 or 6 months people can evolve very malignant stenoses in what initially looked insignificant. If the thallium scan revealed a focal defect, I would probably arrange for catheterization.

Participating Investigators

Ezra A. Amsterdam, MD, Lewis Becker, MD, Peter F. Cohn, MD, Stephen E. Epstein, MD, Milton Hollenberg, MD, Lawrence D. Horwitz, MD, Harold L. Kennedy, MD, MPH, Mitchell Krucoff, MD, Joel Kupersmith, MD, William W. Parmley, MD, and Carl J. Pepine, MD.

Group Discussion: Relevancy of Silent Myocardial Ischemia to the Practicing Physician

Dr. Kennedy (*St. Louis, Missouri*): Most practicing clinicians realize that exercise testing has been used for 15 to 20 years and are comfortable using it in various situations. There can't be much discussion about ambulatory monitoring in the setting of silent myocardial ischemia because it has only been applied to prove that asymptomatic ischemia exists, and this predominantly in physiologic studies. Only in the next 5 to 10 years will ambulatory monitoring for asymptomatic ischemia evolve in clinical use. Is each of you going to feel comfortable that ambulatory monitoring will actually do this, or that we will really be able to interpret the results accurately? Full knowledge of this technique, including interpretation of the data it provides in the setting of silent ischemia, is still evolving.

Dr. Cohn (*Stony Brook, New York*): Perhaps that's a good starting point for some discussion on the relevancy of silent ischemia to the practicing physician. It's obvious that in the years ahead, when we talk about silent ischemia, it will be about Holter findings in addition to the treadmill test. We are going to have to start feeling more comfortable with the Holter, in terms of telling practicing physicians about it. How can we best use the Holter, and in what kind of situation is it most appropriate and useful? I think that for the totally asymptomatic patient, the Holter has no value as a screening procedure at the present time. The exercise test does. In research centers, the Holter might be used for further risk stratification, but that's a limited area. Certainly in the post-infarction patient, the exercise test is still very important. Though, again, in those patients who can't exercise, there seems to be a role for the Holter. Certainly in the patient with angina, the Holter seems to be the most useful. Since we'll be talking in terms of practicing physicians, perhaps we should be addressing this issue now. Dr. Kennedy gave us his viewpoint. What do others think?

Dr. Lauler (*New London, Connecticut*): Perhaps I could generalize the discussion here a bit. Dr. Cohn, you and Dr. Kennedy both talked about the challenge of transmitting information about silent ischemia from the realm of investigation to the "real world" of the clinician. The practicing physician is very conservative. He's going to weigh benefit vs risk, and is going to be very reluctant to treat an asymptomatic group. All we need to do is look at the history of hypertension. I can recall an assistant dean at a well-known northeastern medical school who, 25 years ago, elected not to take antihypertensive therapy because he was asymptomatic and because of the side effects of the drugs. He later had a stroke with massive central nervous system damage, but at the time he thought that declining treatment was a valid option. It's a difficult challenge in the totally asymptomatic group. As we look at the practicing physician, the cost factor is an important consideration; perhaps not so much in terms of drug therapy as because of the high cost of technology. As I listen to discussions about Holters, repeat Holters, and scanning images, I am concerned that, as we go to capitation costs, the high-tech evaluation of these patients may be more restrictive than those of you on the leading edge of technological research would like. The other side of the coin is that, if it could minimize hospitalization, it would be worthwhile. So, it's a bit of a 2-edged type of endeavor, with the trend toward keeping patients out of the hospital. But the practicing physician is looking for a working definition of silent myocardial ischemia. The currently accepted criterion is more than 1 episode of 1 mm ST-segment depression lasting more than 1 minute.

Dr. Cohn: That was established in an attempt to define what an ischemic episode on a Holter was.

Dr. Lauler: True, but that was a working definition, something that the practicing physician could look at. One of the difficulties I have, on behalf of practicing physicians, is to know what silent myocardial ischemia is objectively. But the data coming out, particularly those on quantitating ischemia, are disturbing.

For the practicing physician, logic and rationale are important, even if later they are not shown to be perfectly correct. This concept of total ischemic burden is a useful one, because in practice, the physician can say that the total ischemic burden is equal to the symptomatic plus the asymptomatic episodes, and that more aggressive treatment is necessary. It may be that, lacking a clear consensus in terms of Holter and other ways of quantitating ischemia, we conceptualize what we mean by silent myocardial ischemia—for instance, that the majority of episodes are silent; that we are missing them in many of the monitoring episodes in the hospital. We are buying time until the concept of total ischemic burden can be more precisely quantitated.

Dr. Kupersmith (*Louisville, Kentucky*): In most of th country, the practicing physician is no longer conservativ when it comes to high-tech medicine. I think there is a ver large potential for abuse of this test, particularly when man physicians have equipment that is not adequate to the task One ought to enter this into the equation. The second point i that ambulatory Holter monitoring has not been validate for use as a diagnostic or screening test. It has some valid tion as a physiologic monitor of the asymptomatic ischem phenomenon, and it appears to have validation as a progno tic index at certain times, though perhaps not always. It ha

very little or no validation in determining therapeutic endpoint. Perhaps one could say that there is some therapeutic value to this test at this time, but one has to be very conservative about recommendations to practicing physicians.

Dr. Krucoff (*Washington, D.C.*): One of the best things about a council like this, though, is that some education from a responsible source has to occur. Because if it doesn't, there are members of the industry who will propel devices that are not validated, that are lucrative in private-practice use, and which have more potential than any other factor to destroy the credibility of all the work done thus far. One of the most important functions that we have before us is to find a way to communicate to the real-world practitioners about the limitations, strengths and risks of these devices, as well as the applications of these technologies, despite the potential financial benefits of using such devices.

Dr. Silber (*Birmingham, Alabama*): Most of the devices that have been used to detect silent myocardial ischemia are not validated. The first step is to validate these systems, especially a real-time system, real-time ST-segment Holter monitoring system in widespread use. To go a step further, only 2 out of all these real-time Holter monitoring systems have 100% retrieval rate, so, with most of the so-called silent ischemic episodes, it's not possible to look at them beat by beat. Several speakers have pointed out how important it is to look not only at the trend, but also at each individual beat. Most of the real-time systems don't give us a chance to look at this. So, I think the first step would be to validate a system, look at the reliability, and not to jump into all these problems.

Dr. Cohn: What you have said is certainly important. I don't think that any of the real-time systems can be recommended unless they (1) have been validated against an FM system, which is still the standard and, (2) allow inspection of the electrocardiographic data, to check what is being called an ischemic event. I think we'd all agree that this type of session is very useful, primarily because it does allow discussions, give and take, with people free to say whatever they want—and in fact, they do. It's obvious that we've come a long way in terms of our knowledge of silent ischemia. The fact that the number of studies in this particular field has expanded is wonderful, because the more we learn, the more we can translate our knowledge into benefits for patients. Studies on silent ischemia are appearing every month in our most prestigious cardiology journals—which would not have happened 5 years ago. It's this dissemination of knowledge that I think will one day soon make silent ischemia accepted as an integral part of ischemic heart disease.

The concept of total ischemic burden is perhaps how the practicing physician, in the future, will think of ischemia: symptomatic episodes, painless episodes, unrecognized infarction, painful infarction—all part of a spectrum. There is no question that the major source of controversy is how important silent ischemia is prognostically and, if we treat ischemia, whether painful or painless, are we going to influence outcome? This is going to be determined by ongoing therapeutic trials which will hopefully give us answers in the course of the next several years. At meetings like today's, we will be discussing the results of such trials and perhaps coming up with positive conclusions. I would be disappointed to learn that alleviating a patient's ischemia, painful or otherwise, has no effect whatsoever on his life-style, morbidity or mortality. This is indeed how it may come out, we don't know yet, but I think that, being physicians, we hope that by doing something positive, we will be doing some good for the patient.